ANNALS OF
INTERNAL MEDICINE

VOLUME 49 JULY, 1958 NUMBER 1

GIANT FOLLICULAR LYMPHOBLASTOMA: ITS TREATMENT WITH RADIOISOTOPES * †

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GIANT follicular lymphoblastoma was first identified as a distinct disease entity by Brill, Baehr and Rosenthal in 1925.[1] Their original description was "benign giant follicle hyperplasia," but they soon recognized that it was, or could become, a malignant lymphoma.[2, 3] Symmers [4] in 1927 described a group of cases with the same findings which he termed "follicular lymphadenopathy." He considered this a benign condition, but later recognized that it is capable of transition into malignant disease of the lymphosarcoma group. Since these original descriptions, there has been a great deal of discussion and disagreement concerning the origin of the disease, and whether it is originally a lymphosarcoma or becomes one later. There is one point of unanimous agreement, however, and that is that the disease is characteristically very sensitive to radiation therapy. Local x-ray to tumor masses has, in the past, been the preferred treatment, particularly when the disease is relatively well localized.[5, 6, 7, 8, 9, 10] With localization to a single focus, surgical eradication or surgery plus x-ray has been used.[11] Radioisotopes have been of definite value in widespread involvement.[12-16, 21]

In 1940, based on our findings in animals and man that P^{32} uptake in neoplastic and lymphomatous tissues was relatively high,[17-20] we treated a patient with giant follicle lymphoblastoma with this isotope.[21] It is the purpose of this paper to present several cases treated with P^{32} since that time

* Received for publication April 29, 1957.
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† This work was supported in part by the Donner Foundation and the Atomic Energy Commission.
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to show the usefulness of this mode of therapy in some cases, and to add the clinical findings in 20 cases (16 followed to their termination) to the general fund of knowledge concerning this condition. We are including all cases that showed the giant follicle pattern histologically, regardless of the degree and type of dedifferentiation present in the original biopsy or occurring later, since, regardless of the relatively benign or malignant appearance of the microscopic picture, the clinical course is eventually "malignant."

Between 1940 and 1955, 20 patients with a biopsy diagnosis of giant follicular lymphoblastoma were seen at the Donner Laboratory. Fourteen of the 20 patients had received x-ray treatment before they were seen by us. Six of these were in the terminal stage of their illness when seen here and had become unresponsive to roentgen therapy. Six patients had not been previously treated.

Sixteen patients received P^{32} therapy (tables 1 and 2). Five patients, who were already x-ray-resistant and obviously in the terminal stages of their illness, showed no response at all. Four of these patients (A. B., S. B., F. B. and E. M.) died within three weeks of receiving P^{32}, and one (A. B. M.) died two months after P^{32} (table 1). Eleven patients with disease less far advanced received one or more courses of P^{32} (table 2). One patient (A. P.*) showed good response to two courses of P^{32}, and after a third course went into a complete remission. She did not receive any x-ray therapy. Three and one-half years after the last course of P^{32}, and four and one-half years after onset, she died of an acute myocardial infarction. Autopsy failed to show any gross or microscopic evidence of giant follicular lymphoblastoma. One patient (J. S. H.), who had previously received x-ray, went into remission after his first course of P^{32} and maintained this remission for two and a half years. The recurrence after this period did not respond to P^{32} and was only partially controlled by x-ray for one year to death. One patient (R. B.) had a good response to each of four courses of P^{32} over a period of four years. At the time the last course was given, he was considered to be in a terminal state. However, the P^{32}, with local x-ray to the lumbar spine, which had metastatic involvement, produced a nearly complete remission that lasted for five more years. Two patients (R. G. and M. M.) had good response to an initial course and fair response to a later course. One patient (E. F.) had a good response to his initial course and is doing well one year later. One patient (H. P.) had a good response to one course of P^{32} but no response to two subsequent courses four months apart. All of these patients were given additional x-ray therapy in an attempt to control the disease. Two patients (R. C. and C. H.) had a fair response which was not sustained, but had fair control with x-ray. One patient (A. S.) received five courses over a four-year period, with partial response to the first four and none to the last. One patient (A. M.)

* Previously reported.[12]

showed a marked bone marrow depression after two courses, with little or no clinical improvement.

Early experiments with radiophosphorus [17-21] showed that P^{32} injected or fed to an animal remains for a period of time in relatively high concentration in rapidly metabolizing tissue such as bone marrow, liver and neoplastic tissue, and that it eventually concentrates in the bone. Consequently, the limiting factor in the treatment of lymphomatous disease is the depressing effect on the hematopoietic tissue. Because of the relatively great penetration of P^{32} beta rays (8 mm. in tissue), normal cells surrounding the cells with a rapid metabolic rate also receive some irradiation. For these reasons, this isotope has been primarily used for inhibition of the growth of neoplastic tissue, rather than for its complete destruction.[13] In an occasional case (such as R. B., A. P. and J. S. H.), the malignant tissue is sufficiently sensitive to radiation that bone marrow depression is minimal in proportion to the effect on the tumor tissue.

The general plan of treatment in the above cases was to administer fairly small doses of P^{32} intravenously at variable intervals to put the disease constantly under control. The hemoglobin concentration and the red cell, platelet and white cell counts were followed closely to determine the degree of bone marrow suppression, and the duration of therapy was determined accordingly. The usual fractional dosage employed was approximately 1 mc., and the usual interval between doses, approximately one week. This was, however, highly individualized, with single doses as high as 5.1 mc. given, and intervals up to two months used. The total dosage given a single patient, successfully treated, varied from 6.0 mc. to 44.3 mc. Among the

TABLE 1

Clinical Course in Terminal Cases*

Patient	Age at Onset	Sex	Duration		Dosage	Duration of Therapy	Condition When Treated
			Before P^{32}	After P^{32}			
1. A. B.	32	M	8 yrs.	6 days	5.1 mc.	1 dose	Marked anemia and leukopenia. Marked adenopathy and splenomegaly.
2. A. B. M.	60	M	4 yrs., 4 mo.	1 mo.	33 mc.	8 weeks	Marked anemia and leukopenia. Generalized adenopathy, splenomegaly, right hydrothorax.
12. S. B.	57	F	8 yrs.	5 days	5.0 mc.	1 dose	Marked anemia with hypoplastic marrow. Marked adenopathy, hydrothorax.
15. F. B.	61	M	4 yrs.	22 days	4.0 mc.	16 days	Moderate anemia. Splenomegaly, adenopathy and hydrothorax.
18. E. M.	51	F	4 yrs.	12 days	3.0 mc.	9 days	Marked anemia. Massive abdominal nodes, ascites, hydrothorax.

* All had become resistant to x-ray treatment.

TABLE 2

Clinical Response to P^{32} Therapy

Patient Age Sex	Course No.	Duration Before P^{32} (months)	Duration After P^{32} (months)	Total Duration (months)	P^{32} Therapy Amount (mc.)	P^{32} Therapy Within period (wks.)	X-ray Before P^{32}	X-ray After P^{32}	Response to P^{32} Duration (months)	Response to P^{32} Nature of Response	Remarks
3. A. P. 65 F	1	12	42		14.1	14	no	no	12	Ascites, edema, abdominal masses disappeared.	Died of myocardial infarction.
	2	24	30		6.5	2	no	no	9	Lymph nodes decreased.	No evidence of giant follicle lymphoblastoma at autopsy.
	3	33	21		23.7	52	no	no	21	Complete remission.	
				54	44.3						
4. R. C. 43 F	1	53	91	144	16.9	20	no	yes	?	Fair. Required x-ray for complete control.	Maintained on local x-ray therapy.
5. A. S. 37 M	1	5	47		9.2	4	no	yes	—	None. Bone marrow depression.	Bone marrow very sensitive to x-ray.
	2	17	35		9.6	4	no	yes			
	3	29	23		3.0 (1 dose)		yes	yes			Had general systemic reactions after therapy.
	4	38	14		3.0 (1 dose)		yes	yes			
	Term.				3.6 (1 dose)		yes				Refractory anemia developed.
				52	28.4						Autopsy showed extensive bone marrow infiltration.
6. A. M. 49 F	1	16	44		7.1	6	yes	yes	—	No response by lymph nodes. Bone marrow depression.	Good response to subsequent x-ray.
	2	29	31		8.6	6	yes	yes	—	Same.	
				60	15.7						
7. R. B. 55 M	1	7	111		10.5	8	no	yes	8	Good response. Reduction of lymph nodes and spleen.	Received local x-ray 9 mos. after 1st course.
	2	29	89		2.1 (1 dose)		yes	yes	7	Same.	Thought to be terminal at time of last course. Local x-ray to spine after last course. No response to Teropterin or x-ray in terminal illness.
	3	36	82		4.1	16	yes	yes	15	Same.	
	4	53	65		3.0	2	yes	yes	60	Same. Relief of back pain.	
				118	19.7						

TABLE 2—*Continued*

Patient Age Sex	Course No.	Duration Before P^{32} (months)	Duration After P^{32} (months)	Total Duration (months)	P^{32} Therapy Amount (mc.)	P^{32} Therapy Within period (wks.)	X-ray Before P^{32}	X-ray After P^{32}	Response to P^{32} Duration (months)	Response to P^{32} Nature of Respons	Remarks
8. C. H. F	1	42	30	72	6.6	26	yes	yes	6	Fair only. Spleen and lymph nodes decreased, but refractory anemia developed.	Required transfusions and local x-ray for last 2 years of life.
9. J. S. H. 37 M	1	26	50		3.1	8	yes	yes	36	Relief of bone pain. Reduction of spleen. Lymphocytosis to normal.	Excellent response at first. Poor control from subsequent x-ray.
	2	62	14		4.0	4	yes	yes	—	No response.	
				76	7.1						
14. H. P. 55 M	1	16	23		3.0	2	no	yes	8	Reduction of lymph nodes and spleen. Improvement in differential count.	No response to Teropterin after relapse. Colloidal $CrP^{32}O_4$ used for last dose.
	2	28	11		3.0	2	no	yes	—	Poor. Bone marrow depression.	Died suddenly. No autopsy.
	3	32	7		0.5 (1 dose)		yes	yes	—	None. Bone marrow depression.	
				39	6.5						
16. M. M. 40 M	1	57	23		3.0	8	yes	yes	7	Reduction of spleen and liver. Clearing of edema. Differential count from 96% lymphocytes to normal except for 5% prolymphocytes.	Colloidal $CrP^{32}O_4$ used 1st course. Interim treatment with local x-ray to tolerance dose.
	2	74	6		3.0	3	yes	yes	2	Fair, for two months only.	
				80	6.0						
17. R. G. 47 M	1	68	40		4.0	4	yes	yes	20	Good. Decrease in lymph nodes; reduction in absolute lymphocytosis.	Also had hemochromatosis. Lymph node recurrences treated by x-ray after 2d course.
	2	90	18		3.0	3	yes	yes	?	Fair. Reduction in nodes not sustained.	
				108	7.0						
20. E. F. 53 M	1	78	16	94 (to present)	9.4	2.5	yes	yes	16 (to present)	Good response to combined x-ray and P^{32}.	Local x-ray started prior to P^{32}, which was then given concurrently. Patient living and well.

patients who showed the best response, the total dose for one course ranged from 3.05 mc. over a two month period (J. S. H.) to 23.7 mc. over one year (A. P.).

The P^{32} was given in the form of isotonic $Na_2HP^{32}O_4$ in all cases except two. Case M. M., first treated in 1948, was given three 1 mc. doses of colloidal chromic phosphate ($CrP^{32}O_4$) prepared after the method of Jones et al.,[22] in an attempt to localize the radiation in the spleen.[13, 22, 23] The response was very satisfactory in reducing spleen size and controlling the leukemic blood picture. Case H. P. received a single dose of 0.5 mc. $CrP^{32}O_4$ in his terminal illness, with no response after having received two 3 mc. courses of P^{32} five months and 18 months previously, with good response. With rare exceptions, all P^{32} was administered intravenously.

Case Reports

Case 3 (*A. P.*). A 65 year old white housewife first noted painless swelling in her neck. A lymph node biopsy showed giant follicular lymphoblastoma. When we saw her a year later (no treatment having been given in the interim), physical examination showed generalized lymphadenopathy, ascites, irregular abdominal masses, and edema of both legs. Laboratory work showed a red cell count of 3,620,000; hemoglobin, 76%; white cell count, 6,650, with a normal differential. The patient received 14.1 mc. of P^{32} intravenously in approximately 1 mc. doses over a six-week period. The response was very satisfactory, with disappearance of the adenopathy, edema, ascites and abdominal masses. Her hemoglobin dropped to 42%, and the white cell count to 2,500. Transfusions were given and the bone marrow recovered rapidly. One year later there was recurrence of the cervical adenopathy, and she received 6.53 mc. of P^{32} intravenously over a two-week period, one year after the original course. The adenopathy again responded satisfactorily, and there was no significant bone marrow depression. Nine months after the second course the adenopathy had again recurred, and she was started on a third course of P^{32}, receiving a total of 23.7 mc. in approximately 1 mc. doses at two-week intervals. Three years after the first course of therapy she was completely free of any evidence of lymphomatous disease. She continued asymptomatic another six months, when she died suddenly of an acute myocardial infarction. Autopsy revealed no evidence of any malignancy. She received a total of 44.3 mc. of P^{32} in three courses over a period of 21 months with an excellent remission.

Comment: Nine months after completion of the P^{32} therapy there was no evidence of the disease, clinically or by gross and histologic postmortem examination.*

Case 7 (*R. B.*). A 55 year old civil engineer began having "sciatic pain" and weight loss. Because of left chest pain and axillary adenopathy, an axillary node was biopsied, and this showed "giant follicle lymphosarcoma." His liver and spleen were enlarged to the level of the umbilicus. He had not had previous treatment when first seen by us. Examination showed the hepatosplenomegaly and moderate inguinal adenopathy. The red blood cell count was 4,390,000; hemoglobin, 12.9 gm.; white cell

* The fact that this patient apparently showed no evidence of giant follicle lymphoblastoma reminds the authors of the fact that in a series of mice having generalized lymphosarcomatosis and receiving P^{32} therapeutically, approximately 15% of them became free of the disease.[37]

count, 9,400, with 4% prolymphocytes in the differential count. The patient received 10.49 mc. of P^{32} intravenously in doses ranging from 0.58 mc. to 1.19 mc., given twice a week. The lymphadenopathy disappeared, the spleen decreased 4 cm. in size, and the liver decreased slightly. He was subjectively much improved. Six months later the adenopathy had reappeared and the liver and spleen had increased to their former size. He was then given x-ray therapy, 200 r to each of 10 ports over the cervical, axillary and inguinal nodes, and over the mediastinum and upper abdomen. There was fair response to this, but six months later there was again an increase in size of the lymph nodes, liver and spleen, and the x-ray was repeated (400 r to the spleen, 600 r to the liver, 100 r to the right axilla, and 200 r to the left axilla and left groin). The spleen and liver each decreased to 2 cm. below the costal margin. The adenopathy disappeared. This condition was maintained for another year and the patient was subjectively well. He again was given 2.07 mc. of P^{32} intravenously, with further response of the liver and spleen, and after six months these organs were not palpably enlarged. Soon he complained of radicular pain, and x-rays showed a compression fracture of T_{12}. He received 2.13 mc. of P^{32} intravenously, and the back was treated by orthopedic measures. He continued to have back pain throughout the next year, but there was no detectable adenopathy or increase in size of liver and spleen.

After another year he had a marked increase in back pain and a marked weight loss. He was hospitalized, and x-rays showed osteolytic and osteoblastic lesions in T_{12}, L_1, L_5 and the sacrum. Blood counts on February 15, 1946, showed a red cell count of 4,610,000; hemoglobin, 14.5 gm.; white cell count, 6,600, with 2% prolymphocytes and 1% lymphoblasts in the differential count. He was often confused and disoriented. There was some increase in size of the peripheral lymph nodes, but not of the liver and spleen. He was thought to be in a terminal condition. He received P^{32}, 3 mc. intravenously in three weekly doses, with relief of pain by the second dose. He improved rapidly. The differential count returned to normal and he was discharged, able to walk in a Taylor back brace three months later. However, within three months he again had severe exacerbation of back pain, was hospitalized and received x-ray therapy to the lower thoracic and lumbar spine. He developed a moderate anemia, which soon returned to normal. His spleen tip was palpable at this time but it also disappeared. His clinical condition slowly improved and he was dismissed from the hospital with no clinical evidence of the disease other than the bony lesions, which showed some healing by x-ray.

The patient maintained a complete clinical remission for the next four years. He was able to work as a real-estate appraiser. X-rays of the spine showed complete healing of all the lesions, leaving only evidence of old compression fractures of T_{12} and L_5. He again relapsed, with increase in mediastinal lymph nodes and hepatosplenomegaly. He failed to respond to x-ray therapy at this time, and death followed. Autopsy showed extensive involvement of the abdominal organs, lymph nodes and dura mater with "lymphosarcoma, lymphocytic type."

Comment: This case shows an excellent response to combined P^{32} and x-ray treatment after evidence of widespread involvement for five years. The complete clinical remission lasted more than four years before the final uncontrollable relapse occurred.

Clinical Observations

Of the 20 patients in this series, 16 were followed to death, two are still living, and two (who were not treated by us) were lost to follow-up.

TABLE 3

Age of Onset, Sex Ratio, and Duration from Onset in 20 Cases of Giant Follicular Lymphoblastoma

Age	
Average age at onset	48 yrs.
Median age at onset	49 yrs.
Range of age at onset	32 to 65 yrs.
Sex	
Male	12
Female	8
Ratio	1.5 : 1
Duration after onset (16 patients)	
Average	6.1 yrs.
Median	5.5 yrs.
Range	1.8 to 12 yrs.
5 yr. survival	11 of 18 (61%) (one living, one lost)
10 yr. survival	1 of 16 (6.3%)

Age at Onset and Sex: The average age at onset of 48 years, with a median age of 49 years, corresponds to that reported by Gall and Mallory [24] and Gall, Morrison and Scott.[25] The range of ages reported in the literature extends from birth [15] to 80 years.[6] Our series falls in the middle of this span (32 to 65 years), with 70% having onset between the ages of 40 and 55 years, and 85% after 40 years of age. This is in contrast with the experience of Symmers,[6] who found the incidence greatest between the ages of 25 and 40. This comparison may not be justified, however, since Symmers apparently did not include those cases he classified as "polymorphous cell sarcoma," whereas we are including many which would fall into this classification. The sex distribution showed the expected predominance of males over females, in the ratio of 1.5 to 1. This is in general agreement with the ratio of 1.2 to 1 reported by Gall, Morrison and Scott [25] and by Hellwig,[26] and lower than the 2.2 to 1 or greater ratio in lymphosarcomas in general.[24]

Duration: The average duration of 6.1 years is longer than in previously reported series [15, 24–27] (table 3). If we consider only the 15 patients who were treated with P^{32} and who have since died, the average duration is 6.4 years. With the elimination of the five cases who were considered terminal when P^{32} therapy was initiated, the average duration for the remaining 10 cases rises to 6.7 years. Further, excluding patient A. P., who died of an

TABLE 4

Initial or Presenting Involvement in 20 Cases

Cervical nodes only	11 cases
Supraclavicular node only	1
Submandibular node only	1
Inguinal nodes only	1
Generalized adenopathy	3
Generalized adenopathy and bony destruction	1
Testicular mass	1
Skin and axillary nodes	1

TABLE 5

Organ Involvement and Clinical Findings

	Number	%
Peripheral lymphadenopathy	20	100
(With splenomegaly)	17	85
(With hepatomegaly)	8	40
Hydrothorax	8	40
Ascites	6	30
Peripheral edema	3	15
Cutaneous infiltration	4	20
Discrete bony destruction	3	15
Bone marrow invasion	6	30
Genitourinary	2	10
Testicle	1	5
Prostate	2	10
Bladder	1	5

unrelated cause and showed no gross or microscopic evidence of the disease at autopsy, the average duration for nine adequately treated cases becomes 6.9 years. Although there are rare cases of long survival (14[15] to 22[28] years) in the literature, and the 10-year survival rates reported range from 11% to 16%,[24] only one of our patients survived more than 10 years. Our five-year survival rate of 61% is better than that previously reported (36.8% to 53%).[7, 24-26]

Presenting Lesions and Organ Involvement: The location of the initial presenting lesions is demonstrated in table 4. The initial cervical node involvement in 11 of 22 cases is similar to the incidence reported by Uhlmann [8] in 10 of 22 cases. All in our series showed fairly generalized lymph node involvement at some time during the course of the disease before they were first seen at this clinic. The organ involvement and clinical findings are summarized in table 5.

Skin: One patient first noted an erythematous, slightly raised rash of her face, neck and back, followed shortly by axillary adenopathy. Biopsy of the lesion showed "lymphadenosis cutis" and giant follicular lymphoblastoma of the axillary nodes. Three other patients developed cutaneous nodular lesions. One patient showed giant follicular lymphoblastoma of the skin on biopsy. The other two were not biopsied, but the nodules disappeared after local x-ray therapy. There were no cases of chronic dermatitis associated with this series, such as reported by Combes and Bluefarb [29] and Symmers.[6]

Bone and Bone Marrow: Three patients had discrete destructive lesions in the bone, two in the lumbar spine and one in the pelvic girdle. These all responded well to P^{32} or local x-ray therapy. On bone marrow aspiration, six patients showed evidence of marrow invasion. This was moderate in two cases and fairly extensive in four cases. One case, M. M., who had the clinical and biopsy picture of chronic lymphatic leukemia developing 10 months after the original biopsy diagnosis of giant follicle lymphoblastoma, had a large number of "notched nucleus cells" [30, 31] or "hematogones" [27, 32, 33] in the marrow aspiration, although none was noted in the peripheral blood.

TABLE 6

Hematologic Abnormalities

	Number	% of 16 Patients
Anemia	14	87.5%
Mild	1 (no splenomegaly)	6.25%
Moderate	3 (with splenomegaly)	18.75%
Severe	10 (with splenomegaly)	62.5%
Leukopenia	11 (9 with splenomegaly)	68.75%
Leukopenia and anemia	9 (all with splenomegaly)	56.25%
"Lymphemia" (absolute lymphocytosis)	3	18.75%

Peripheral Blood: Fourteen of the 16 patients followed to termination were anemic (table 6). The remaining two patients died in distant places, and the follow-up letters made no note of anemia. Three patients had a moderate anemia, not requiring transfusions. In two of these the cause was irradiation or bone marrow invasion, or a combination of both. Ten patients were severely anemic and required transfusions. In three patients the relation to P^{32} or x-ray therapy was clear; two later recovered. In two patients the cause was irradiation and bone marrow invasion. Two patients had aplastic bone marrows. Both had become refractory to x-ray and were terminal when P^{32} therapy was begun. In only three patients was the cause of the anemia not clear. These patients were not considered, at the time of observation or treatment, to have manifestations of "hypersplenism." In none of our series did the bone marrow show a "compensatory hyperplasia," as described by Evans and Doan.[15] However, the majority of our cases had considerable x-ray or P^{32} therapy, which may have interfered with the ability of the marrow to compensate. Only one patient, R. G., had clinical icterus. He had a slight anemia (red blood cell count, 3,900,000). He had been treated with intravenous iron before being seen at this clinic, and had developed hemochromatosis. His spleen was not involved or enlarged at autopsy. Eleven patients also showed a leukopenia. This also was considered to be a result of irradiation or bone marrow invasion, or both, in all cases.

Six of the 20 patients had abnormal lymphocytes (lymphoblasts or prolymphocytes, or both) in the circulating blood. Three of these had absolute lymphocytosis or "lymphemia." One case described above (M. M.) had a typical chronic lymphatic leukemia. In the other two, the "lymphemia" responded to the P^{32} therapy, as did the lymph nodes and spleen.

The two patients still living have not shown anemia or abnormalities of the leukocytes.

PATHOLOGIC OBSERVATIONS

The histologic variations and alterations of giant follicular lymphoblastoma, and its types or derivatives as frequently reported in the literature,[6, 24, 34–36] were observed in our series. The original biopsy diagnosis in 11 cases was the "benign" giant follicular lymphoblastoma (or giant follicle

hyperplasia). Nine cases showed some dedifferentiation in the original biopsy (Gall, Morrison and Scott Types III and IV, giant follicle lymphosarcoma, polymorphous cell sarcoma arising from giant follicular lymphoblastoma of Symmers, or follicular reticulosarcoma of Robb-Smith), variously labeled by various pathologists but all showing the giant follicle pattern.

Eight patients had a single diagnostic biopsy, without a second specimen having been taken. Four of these were histologically "benign" giant follicular lymphoblastoma, and four presented a more dedifferentiated picture with the underlying giant follicle pattern.

Twelve patients had a second biopsy and/or an autopsy (table 7). The interval between obtaining these specimens varied from two months to nine years and four months. However, the interval from the original to the final specimen was not less than 19 months in any one patient.

Seven patients with two or more histologic specimens had the original diagnosis of giant follicular lymphoblastoma, Type I or II. Two are still living and doing well, with no change demonstrated in repeated biopsy at two years and three years, respectively. One patient, who died of unrelated disease, showed no evidence of giant follicle lymphoblastoma or of any other malignancy. One patient showed no change in biopsies 20 months apart, but died suddenly 10 months after the last biopsy. No autopsy was obtained. Three patients later showed dedifferentiation to a histologically more malignant disease. One developed a generalized small-cell lymphosarcoma, and two developed reticulum cell sarcoma.

Five patients with multiple histologic specimens showed some degree of dedifferentiation already present in the original biopsy. Three of these maintained the same histologic picture at autopsy one year and seven months, six years, and eight years and three months, respectively, after the original diagnosis. One developed a small-cell lymphosarcoma, and one developed a typical clinical and hematologic chronic lymphatic leukemia. Autopsy confirmed the clinical findings of small-cell lymphosarcoma or chronic lymphatic leukemia. None of the patients in this series developed Hodgkin's disease.

The relatively benign or malignant histologic picture of the original biopsy appeared to have little relation to the life expectancy in this series. Of the 11 patients with the original diagnosis of "benign" giant follicular lymphoblastoma, 2 are living 3.5 and 6.5 years, respectively, after onset of symptoms, and two have been lost to follow-up. The average duration of disease in the remaining seven was 4.9 years, and the median, 4.5 years. The range was from 3.3 years to 8 years. On the other hand, the average duration in the nine patients showing originally a more malignant histologic picture was 7.0 years, median, 6.5 years, and range, 1.8 to 12 years.

Changes in the histologic picture between the original biopsy and the autopsy findings also failed to correlate with duration of the disease. The

TABLE 7

Results of Multiple Biopsies

Patient	Nature of Material	Interval Between Specimens (months)	Pathologic Diagnosis*	Remarks
I. Variation in Histologic Structure				
A. Original biopsy, giant follicular lymphoblastoma				
1. A. B.	lymph node		Giant follicular lymphoblastoma	Treated terminally.
	skin	84	Giant follicular lymphoblastoma	No response to P^{32}.
	autopsy	12	Generalized small cell lymphosarcoma	Total duration, 8 years.
2. A. B. M.	lymph node		Giant follicular lymphoblastoma	Total duration, 4.5 years.
	autopsy	52	Reticulum cell sarcoma	
11. J. H.	lymph node		Giant follicular lymphoblastoma	Lost to follow-up.
	lymph node	51	Reticulum cell lymphosarcoma	
B. Original biopsy showing dedifferentiation				
4. R. C.	lymph node		Giant follicular lymphosarcoma	Total duration, 12 years.
	autopsy	112	Lymphosarcoma, small cell type	
16. M. M.	lymph node		Giant follicular lymphosarcoma	Total duration, 6.5 years.
	lymph node	10	Small cell lymphosarcoma or lymphatic leukemia	
	autopsy	29	Small cell lymphosarcoma or lymphatic leukemia	
II. Original Histological Structure Unchanged				
A. Original biopsy, giant follicular lymphoblastoma				
3. A. P.	lymph node		Giant follicular lymphoblastoma	Died of acute myocardial infarction.
	autopsy	48	No evidence of malignancy	Total duration, 4.5 years.
14. H. P.	lymph node		Giant follicular lymphoma	Died suddenly 10 months after 2d biopsy. No autopsy.
	lymph node	20	Giant follicular lymphoma	Total duration, 3.25 years.
19. M. T.	lymph node		Giant follicular lymphoblastoma	Living.
	lymph node	25	Giant follicular lymphoblastoma	
20. E. F.	lymph node		Giant follicular lymphoblastoma	Living.
	lymph node	36	Giant follicular lymphoblastoma	
B. Original biopsy showing dedifferentiation				
5. A. S.	lymph node		Giant follicular lymphosarcoma	Autopsy showed increased invasion but no further histologic dedifferentiation.
	lymph node	2	Giant follicular lymphosarcoma	
	autopsy	48	Giant follicular lymphosarcoma	Total duration, 4.33 years.
13. O. W.	lymph node		Giant follicular lymphoblastoma, Gall Type IV	Total duration, 1.83 years.
	lymph node	5	Giant follicular lymphoblastoma, Gall Type IV	
	autopsy	14	Giant follicular lymphoblastoma, Gall Type IV	
17. R. G.	lymph node		Giant follicular lymphosarcoma	Also had hemochromatosis.
	autopsy	99	Giant follicular lymphosarcoma	Total duration, 9 years.

*In cases where the pathologic specimen was unavailable for review, the original diagnosis is given.

average duration in four patients who maintained the same picture was 4.9 years, whereas in four patients who showed further dedifferentiation the duration averaged 7.8 years (table 7).

Autopsies were performed in eight patients. In one there was no evidence of lymphoma. One patient died elsewhere, and a complete autopsy

TABLE 8

Autopsy Findings (Six Cases)

Lymphomatous involvement of:	
Lymph nodes	6
Peripheral	5
Mediastinal	5
Retroperitoneal	5
Abdominal	4
Spleen	3
Liver	4
Gastrointestinal tract	2
Genitourinary tract	2
Lungs	2
Pancreas	2
Bone marrow	1
Meninges (cerebral)	1

report was not obtained. The final diagnosis was "lymphosarcoma, generalized." The autopsy findings in the remaining six cases are summarized in table 8.

One patient had a moderately enlarged spleen which was hemorrhagic and congested but showed no lymphomatous involvement. This was associated with necrotic tumor in the liver, and involvement of the stomach and pancreas. The stomach lesion was eroded through the mucosa and was ulcerated. There were no clinical symptoms of this ulcer. The other gastrointestinal lesion involved the colon. The urinary tract was involved, with direct invasion of a kidney in one case and invasion of the prostate and bladder in another.

SUMMARY

The clinical and pathologic findings in 20 patients with giant follicular lymphoblastoma are presented and discussed. The clinical findings correspond well to those previously reported in the literature. There is a marked lack of correlation, in this series, between the duration of the disease and the relative benign or malignant appearance of the lesions histologically.

Sixteen patients who received radioactive phosphorus are presented in summary. Five patients received this therapy while in the terminal stage of their illness. Eleven patients received adequate P^{32} therapy. Three patients showed excellent responses, one showing complete and two nearly complete remission. Three patients had good responses, with duration of control from seven to 20 months. Three patients had fair response but required additional local x-ray therapy for control. The average duration of the disease in the 10 adequately treated cases followed to termination was 6.7 years, compared to the average duration of 6.0 years or less reported in the literature.

Radioactive phosphorus with local x-ray, or alone, may be the treatment of choice in giant follicular lymphoblastoma and certainly merits serious consideration, particularly in those cases with widespread involvement.

SUMMARIO IN INTERLINGUA

Es presentate e discutite le constatationes clinic e pathologic in 20 patientes con lymphoblastoma gigantofollicular. In 15 casos, le affection initial concerneva un sol gruppo de nodulos lymphatic. In 11 inter ille 15 casos, il esseva le nodos cervical que esseva afficite le primes. Omne le casos exhibiva in le curso del tempore un lymphadenopathia satis general. Splenomegalia esseva presente in 17 casos, hepatomegalia in octo. Anemia esseva presente in 14 casos, leucopenia in 11. Tres patientes monstrava un lymphocytose absolute. Un de illes presentava un typic aspecto de chronic leucemia lymphatic. Le distribution per sexo esseva 12 masculos e octo femininas. Le etate medie al tempore del declaration esseva 48,1 annos. In 16 casos, le duration medie esseva 6,07 annos. Le superviventia quinquenne pro 18 casos esseva 61,1%; le superviventia decenne pro le mesme gruppo esseva 6,25%.

Esseva constatate non-correlation del duration del morbo con le relative apparentia benigne o maligne del lesion ab le puncto de vista histologic. Le duration medie in septe patientes, in qui le diagnose bioptic original habeva essite "benigne" lymphoblastoma gigantofollicular, esseva 4,9 annos. Le duration medie in 9 patientes con un aspecto originalmente plus maligne esseva 6,98 annos. Alterationes in le aspecto histologic inter le tempore del biopsia original e del necropsia non esseva correlationate al duration del morbo. In quatro patientes sin alteration del aspecto histologic, le duration medie esseva 4,92 annos, durante que in quatro patientes qui monstrava un dedifferentiation additional le duration medie esseva 7,75 annos.

Dece-sex patientes esseva tractate con phosphoro radioactive. Cinque de illes se monstrava resistente a radios X e se trovava in stato terminal quando le tractamento a P^{32} esseva initiate. Dece-un patientes recipeva le therapia a P^{32} in forma adequate, sol o combinate con local radios X. Le plano general del tractamento esseva administrar satis micre doses de P^{32} per via intravenose a intervallos variabile pro fortiar le morbo sub control. Le dosage fractional esseva circa 1 mc, le intervallo usual inter le doses circa un septimana. Sed le valores esseva individualisate a grados extreme. Le doses individual variava usque a un maximo de 5,1 mc e le intervallos inter le doses usque a duo menses. Esseva mantenite un constante controlo del concentration de hemoglobina e del numeration de erythrocytos, plachettas, e leucocytos, a fin de determinar le grado del suppression del medulla ossee, e le duration del therapia esseva adjustate correspondentemente.

In tres patientes le responsa esseva considerate como excellente. Un de illes monstrava remission complete. In le duo alteres le remission esseva quasi complete. In tres altere patientes le responsas esseva bon, con domination del morbo durante septe a 12 menses post un sol curso del therapia. In le proxime tres patientes le responsa esseva satis bon, sed pro dominar le morbo, le addition de local radios X esseva requirite. Le duration medie in 10 casos, in que le tractamento esseva adequate e que remaneva sub observation usque al fin, esseva 6,67 annos.

Phosphoro radioactive, con local radios X o sol, es possibilemente le tractamento de election in lymphoblastoma gigantofollicular e certo merita le plus serie consideration, specialmente in casos in que le affection es extense.

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ALLERGIC REACTIONS TO TRANQUILIZING DRUGS *

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Tranquilizing drugs, like most others, may act as allergens. Three classes of tranquilizing drugs have been widely used and allergic reactions reported from their use. These classes of drugs are: (a) the phenothiazine derivatives, notably chlorpromazine, (b) the Rauwolfia alkaloids, notably reserpine, and (c) the substituted propanediols or butanediols, notably meprobamate. In the case of the first and third classes of drugs, allergic reactions account for the major complications encountered.

Phenothiazine Derivatives (Chlorpromazine, Promazine, Triflupromazine, Mepazine, Proclorperazine, Perphenazine)

Agranulocytosis: The most serious complication produced by these drugs is agranulocytosis, although it is fortunately rare. Due to the exceptionally wide use of chlorpromazine throughout the world, most of the cases recorded have been due to this drug. A little more than a year ago it was estimated that only 50 cases of agranulocytosis due to chlorpromazine had appeared.[1] Since then a few additional reports have appeared in the literature. In a review of 30 case reports, the pertinent clinical and laboratory characteristics are noted in table 1.

With only a few exceptions, most of the patients have been women, and most of those affected past 50 years of age. A definite time period has been noted during which the reaction may occur. Although cases have occurred as early as one week and as late as 11 weeks after beginning treatment, the majority occur in the sixth to eighth week. Neither the daily dose (which has varied from 50 to 1,000 mg.) nor the total dose (from less than 3 gm. to more than 14 gm.) has been an important factor. The clinical onset has usually been abrupt, with fever and sore throat the predominant signs. Necrotic skin or mucous membrane lesions and cervical adenopathy have also been frequently noted. One third of the reported cases have been fatal. Recovery has occurred despite reduction of the total leukocyte count to as low as 120 per cubic milliliter, and death has occurred with a total leukocyte count as high as 2,800 (but with only 3% polymorphonuclears). In most cases the total white cell count has declined to between 400 and 900

* Received for publication September 26, 1957.
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TABLE 1

Clinical and Laboratory Characteristics of Agranulocytosis Due to Chlorpromazine: 30 Case Reports

Age of Patient	
Under 50 years	6
Over 50 years	19
Not stated	5
Sex of Patient	
Male	4
Female	22
Not stated	4
Daily Dose of Drug at Time of Onset	
300 mg. or less	15
More than 300 mg.	4
Not stated	11
Duration of Treatment at Time of Onset	
3 weeks or less	4
4 to 8 weeks	21
More than 8 weeks	3
Not stated	2
Lowest Total White Cell Count	
Less than 400 cu. ml.	4
400–900 cu. ml.	16
More than 900 cu. ml.	3
Not stated	7
Clinical Signs—19 patients with adequate data	
Fever	19
Sore throat	15
Skin or mucous membrane	5
Fate	
Recovered	20
Died	10

cells, with a virtual absence of neutrophils. Bone marrow examinations in 13 cases have consistently shown a picture of granulocytic maturation arrest. In one case platelets were reduced to 66,000 per cubic milliliter, although other hematopoietic systems are not ordinarily affected. Treatment has usually consisted of antibiotics, adrenocortical hormones and blood transfusions. Death has commonly been due to complicating infection or acute heart failure (in some instances possibly precipitated by steroids or blood replacement).

In six cases other evidence of allergy was present at the time of onset of agranulocytosis: four had jaundice and two had skin rashes. Although an immunologic mechanism is strongly suspected as the cause of agranulocytosis, attempts at demonstrating leukocyte agglutinins have been fruitless.[2] In one case, agranulocytosis was successfully reproduced by retreatment with chlorpromazine.[3] In another, retreatment for 60 days with 10 mg. daily failed to elicit leukopenia.[4]

Data are presented in table 2 from our most severe case of leukopenia

among more than 1,500 patients treated with chlorpromazine. During the ninth week of his first course of treatment this patient had a low absolute count of neutrophils. When treated again the count fell to still lower levels in the fourth week. In both instances recovery was prompt with discontinuation of the drug. On each occasion the decline in neutrophil count was gradual, suggesting that periodic leukocyte counts during the first several weeks of treatment may serve a useful purpose. The positive challenge test makes us feel that this patient was definitely sensitive to chlorpromazine, though an attempt to demonstrate leukocyte agglutinins on March 1, 1957, was unsuccessful.

Two cases of agranulocytosis due to promazine [5, 6] and one due to mepazine [7] have been reported which are similar in all respects to those from chlorpromazine. At least two other phenothiazine derivatives (better known as antihistaminics than as tranquilizing drugs) have also produced agranulocytosis. Possible agranulocytosis should be anticipated from any phenothiazine derivative. However, despite ample use, no such cases have yet been reported from perphenazine or proclorperazine.

Jaundice: Jaundice is a more frequent complication of chlorpromazine therapy than is agranulocytosis, but is less feared. The prevalence of jaundice is difficult to estimate, though it probably lies between 1 and 3% of patients treated for a week or more with the drug.[8] In addition, "hepatitis" manifested by liver enlargement or tenderness, fever, abnormal hepatic function tests or histologic evidence of "allergic cholangiolitis" may occur without clinical jaundice. In one series of 50 psychiatric patients treated with chlorpromazine, 21 showed abnormalities in hepatic tests during the first month of treatment, though only one had frank jaundice.[9] Most of the observed abnormalities were transient and cleared with either continued treatment or discontinuation of the drug.

TABLE 2

Serial Total White Cell Counts and Absolute Neutrophil Counts in a Patient Treated with Chlorpromazine on Two Occasions

Date	Total WBC	Absolute Neut.	Treatment
11–1–56	7,000	4,620	CP 200 mg. 12–10–56 300 mg. 12–17–56 400 mg. 12–24–56
12–31–56	4,650	2,790	
1–2–57	5,000	2,500	
1–4–57	3,050	1,260	CP stopped 1–4–57
1–7–57	6,450	3,970	
1–28–57	12,600	10,000	
1–31–57	5,000	2,850	CP 400 mg. 1–31–57
2–4–57	7,300	4,450	
2–7–57	7,000	2,800	
2–25–57	5,000	1,750	
2–27–57	2,425	810	CP stopped 2–27–57
2–28–57	6,700	3,350	
3–1–57	6,000	3,660	

A considerable number of case reports of chlorpromazine jaundice have appeared, with some series as large as 17 to 20 cases.[10, 11] The clinical descriptions have followed a similar pattern, the outstanding features being presented in summary form in table 3. The jaundice is of the intrahepatic obstructive type, frequently accompanied by prodromal symptoms and usually following a benign course. Short-term follow-up studies indicate little residual liver damage, but longer follow-ups will be required to establish such a conclusion.

Although jaundice is an uncommon manifestation of drug allergy, other drugs (arsphenamine, methyltestosterone) have produced a clinically and

TABLE 3

Clinical and Laboratory Characteristics of Jaundice Due to Chlorpromazine: Summary of Data from Reported Cases

Possible Precipitating Factors
Older patients tend to be affected more often
No predilection for a particular sex
No relationship to previous liver damage
Occasional past history of drug reactions or clinical allergies
No relationship to daily dose of drug or total dose
80–90% of cases discovered in first four weeks
Clinical Features
Prodrome of fever, gastrointestinal symptoms, malaise common
Liver enlargement and tenderness, pruritus variable
Patients usually feel better with onset of jaundice
Right upper quadrant pain has led to cholecystectomy
Usual course is self-limited
Fatalities uncommon, usually complicated by other conditions
Some cases seem to respond dramatically to adrenocortical hormones
Usual case shows little residual liver damage
Laboratory Features
BSP retention, elevated alkaline phosphatase or SGO-T titer may precede clinical jaundice
Direct-reacting bilirubin chiefly elevated
Bilirubinuria early; urobilinogenuria later
Transient elevations of serum lipids
Positive flocculation tests may occur, usually transient
Eosinophilia may accompany jaundice
Characteristic biopsy findings: bile plugs in canaliculi, cellular infiltrate in periportal areas, bile-staining of adjacent hepatic cells

histologically similar biliary disturbance. In the case of chlorpromazine, the other allergenic attributes of the drug, the characteristic time of onset early in treatment, and the occasional appearance of concomitant eosinophilia in the peripheral blood or periportal spaces have all suggested that jaundice is due to an allergic reaction.

The most convincing evidence for an allergic basis of chlorpromazine jaundice is its prompt recurrence upon challenge with the drug. A number of observers have reported such positive challenge tests.[10, 12–14] In my series I have been able to obtain a positive challenge test in nine of 14 attempts even as long as 17 months after the first appearance of jaundice. On the other hand, some patients apparently lose their sensitivity early. In one

case I was able to "desensitize" a patient who reacted to the initial challenge positively by giving small daily doses with slow increments for several weeks.

In table 4 the results of challenge tests to chlorpromazine and promazine are shown in two of our patients. Promazine was selected for the comparative challenge test since it differs from chlorpromazine only in lacking a single chlorine atom on the phenothiazine nucleus. It was reasoned that if cross-sensitivity existed among phenothiazine derivatives, it should be easily demonstrated in the case of these two closely related drugs. Surprisingly, no cross-sensitivity was demonstrated in seven such trials. Similar

TABLE 4

Challenge Tests with Chlorpromazine and Promazine in Two Patients with Chlorpromazine Jaundice

Date	Hepatic Tests			Antecedent Medication and Concomitant Symptoms
	Serum Bilirubin Total (Direct), mg. per 100 ml.	Alkaline Phosphatase, Bodansky units	BSP Retention, 5 mg./K./45 min.	
W. B.				
7–22–55	1.3 (.80)	5.7		CP 200 mg. 7–12 to 7–22–55 Fever, malaise 7–20–55
7–25–55	0.44	5.0		
3–12–56	0.36			
3–14–56	4.75 (2.7)	4.6	55%	CP 200 mg. 3–13 to 3–14–56 Fever, vomiting 3–14–56
3–21–56	1.51	9.7		
3–28–56	0.55	5.8		
5–8–56	0.84		2%	P 800 mg. 5–8 to 5–10–56
5–10–56	0.71	3.2		
9–7–56	4.4 (2.7)			CP 100 mg. single dose 9–6–56 Fever, malaise 9–6–56
11–15–56	0.32		3.4%	
J. F.				
6–23–56	2.48 (1.77)	6.8		CP 200 mg. 6–12 to 6–22–56 Fever, pruritus, vomiting
7–9–56	0.32	3.2		
7–14–56	0.36	2.6	3.4%	P 300 mg. 7–10 to 7–14–56
7–18–56	0.67	7.0	27%	CP 150 mg. 7–17–56 Vomiting for next several days
7–25–56	0.44	4.3	2.5%	

tests for cross-sensitivity between chlorpromazine and promazine produced one positive challenge test to promazine from three trials in patients with chlorpromazine sensitivity.[14] Another report describes jaundice following intramuscular promazine 18 days after a two-week course of chlorpromazine.[15] It is possible, therefore, that some cross-sensitivity may exist between these two drugs, but it appears that it is uncommon and contingent upon prior sensitization to chlorpromazine.

A report of chlorpromazine jaundice after a single oral dose of the drug has also raised the question of cross-sensitivity with other phenothiazines, possibly the antihistaminic drug, promethazine (Phenergan).[13]

I have seen two patients recently whose jaundice appeared within the first two to three days of treatment. Both were alcoholics with anxiety reactions. It is quite likely that they had previously received chlorpromazine without being aware of it. At this writing, no cases have been reported of jaundice from proclorperazine or perphenazine, despite their increasing use. Two cases of jaundice due to mepazine have been reported in a series of 130 patients treated with the drug.[16] These cases appeared to be entirely similar to those of chlorpromazine jaundice.

Dermatitis: Three types of skin eruptions are associated with chlorpromazine sensitivity. First, a systemic sensitization manifested by generalized eruptions described as maculopapular, urticarial, petechial, edematous, bullous and others. This reaction is analogous to jaundice in time of onset, appearing usually from the ninth to the thirty-seventh day of treatment. From 3 to 12% of treated patients may be involved.[17] The rash clears promptly with discontinuation of the drug and does not usually return when the drug is started again. Second, contact dermatitis may occur on the hands of nurses or other hospital personnel handling the drug. Patch tests to chlorpromazine are usually positive. Cross-sensitivity with promazine by patch tests was reported in one case,[18] but in another series of cases no cross-reactions with other phenothiazines could be demonstrated.[19] The third type of reaction is a photosensitive dermatitis affecting the exposed areas. Ordinarily this eruption resembles sunburn, but may be accompanied by edema, vesiculation or petechiae. Like photosensitivity to phenothiazine, the drug must be ingested to produce this reaction. If the drug is applied externally, the photosensitive reaction may be prevented.

Other Allergic Reactions: Fever occurring early in the course of chlorpromazine therapy may herald the appearance of jaundice or agranulocytosis. Many times, fever appears as an isolated finding, often as a sharp spike to 102 to 103° F. and lasting only 12 to 24 hours. Most observers have considered this to be a sensitivity reaction to the drug but have continued treatment.

Eosinophilia is often noted during the first few weeks of treatment. Like fever, it may or may not be associated with other evidence of allergy. In one series, eosinophilia occurred in 29 of 50 patients, 13 of whom had laboratory evidence of impaired liver function.[9] The number of eosinophils in the peripheral blood may be quite high, usually arousing a suspicion of parasitic infestation unless the relationship to the drug is considered. In table 5 the course of eosinophilia in two patients treated with chlorpromazine and one patient treated with proclorperazine is charted.

One case of nonthrombopenic purpura from chlorpromazine has been reported. The complication appeared after 27 days of treatment. The capillary fragility test was positive but the platelet count, bone marrow examination and bleeding tests were all normal. Purpura recurred 33 days after the drug was started again.

TABLE 5

Eosinophilia with Administration of Chlorpromazine and Proclorperazine

Case	Date	Total Leukocyte Count	Per Cent Eosinophils	Drug/Daily Dose
No. 1	6–13–57	7,200	1	CP/150 to 400 mg.
	6–27–57	10,400	1	
	7–5–57	8,500	4	
	7–18–57	12,300	41	
	7–19–57	12,500	40	CP stopped
	7–23–57	11,200	29	
	7–26–57	7,700	18	
	8–5–57	4,500	9	
	8–9–57	6,200	9	
	8–16–57	7,800	1	
	8–22–57	8,400	0	
No. 2	6–20–57	13,500	5	CP/300 mg. 6–19 to 6–21;
	6–27–57	16,600	14	stopped because of fever,
	7–3–57	10,900	10	facial swelling. Resumed
	7–10–57	8,900	8	300 mg. daily on 6–27
	7–18–57	6,800	14	
	7–25–57	10,700	10	
	8–1–57	8,800	11	
	8–8–57	9,100	10	
	8–15–57	11,400	7	CP stopped
	8–22–57	7,700	4	
No. 3	3–26–57	9,900	0	
	4–1–57	7,800	1	PCP/50 mg. to 100 mg.
	4–25–57	9,000	12	
	5–2–57	6,750	26	PCP stopped
	5–7–57	10,000	15	
	5–28–57	7,850	2	

Various reports of asthma associated with chlorpromazine therapy have appeared. Usually the authors have not been specific in documenting the exact relationship of the drug to the asthmatic attack or to the existence of previous asthma. I have not observed any causal effect of chlorpromazine in producing asthma or any aggravation of bronchial asthma by its concurrent use. A single case of severe laryngeal edema with respiratory obstruction has been reported from chlorpromazine. I have observed oral membrane reddening and edema which I attributed to a local sensitivity from holding the tablet too long in the mouth.

RAUWOLFIA ALKALOIDS (RESERPINE)

Despite their vast use, the Rauwolfia alkaloids have caused so few allergic reactions that their allergenicity may be questioned. Only one report of angioneurotic edema has been published, though urticaria has been mentioned rarely.[20] Dr. C. Russell Anderson, of Beverly Hills, California, has told me that he has seen photosensitive dermatitis from reserpine, which cleared slowly over a three-month period. Reserpine is also said to aggravate bronchial asthma, but this effect may be due to its cholinergic-like action.

We have had one unexpected death from reserpine in which the possi-

bility of immunologic thrombocytopenia was considered, though no studies could be made to support this concept.

Case Reports

Case 1. The patient was a 38 year old man who had been continually hospitalized for a catatonic schizophrenic reaction since 1943. Except for his psychosis his general health was good, though he was somewhat undernourished. Numerous laboratory examinations during his hospital course were normal.

On August 22, 1955, the patient was started on reserpine, 8 mg. daily for one week, followed by 3 mg. daily thereafter. His course was not much changed until November 8, 1955, when he seemed to be in a catatonic stupor. He refused meals on that day. At 8 p.m. that evening he was observed by another patient to become pale and unconscious. Examination by a physician a few minutes later revealed him to be dead. No marks or signs of injury were noted, except for a bruise on his right arm.

At postmortem examination diffuse purpura was found. Multiple severe hemorrhages of the lungs, spleen and tracheobronchial mucosa were seen. Less severe hemorrhage was present in the intradural space, gastric and duodenal mucosa, and pancreas. Petechial hemorrhages were noted in the pleura, pericardium and renal pelvic mucosa. Microscopic examination confirmed the presence of hemorrhage as well as generalized capillovenous hyperemia, which included the brain.

Shortly after this death we attempted to demonstrate antibodies to reserpine-sensitized platelets from several patients who had been on reserpine for from four to five months. No such antibodies could be demonstrated. Fairly convincing evidence that reserpine can produce immunologic thrombocytopenia appears in a recent German paper.[21] Purpura and a fall in platelet count to 30,000 occurred after three and one-half weeks of treatment with no more than 1 mg. of reserpine daily. Sternal marrow showed megakaryocytic arrest. Infusion of patient's blood to a normal volunteer produced a fall in platelet count from 460,000 to 60,000 in 45 minutes. A challenge test with 1 mg. of reserpine after three weeks produced a prompt fall in platelet count from 140,000 to 20,000. Tests for platelet antibodies in the serum of the patient were negative.

Nonthrombopenic purpura apparently does occur due to reserpine. The following case occurred in the practice of Dr. M. N. Southworth, of Schoolcraft, Michigan.

Case 2. The patient, a middle-aged woman, was started on reserpine, 1.5 mg. daily, on July 28, 1954, for treatment of hypertension of 260/140 mm. of Hg. On September 14, 1954, her blood pressure was unchanged. Large areas of ecchymosis were present on the arms, legs and trunk. The drug was continued. On September 17, 1954, laboratory work as follows was obtained: erythrocyte count, 4.61 million per cubic milliliter; leukocyte count, 8,400 per cubic milliliter, with a normal differential; platelets were described as normal. The drug was continued, with formation of new ecchymoses until January 28, 1955. Reserpine was stopped and ascorbic acid was started. No new ecchymoses appeared. On April 15, 1955, reserpine was started again and new ecchymoses appeared. The drug was stopped on May 6, 1955. No new ecchymoses were noted during the next several months.

Approximately nine months after her last exposure to the drug we obtained a specimen of this woman's serum. No antibodies to reserpine-sensitized platelets were demonstrated at that time. A single case has been reported that is similar to this, where a generalized petechial eruption appeared after six and one-half months of treatment.[22] The rash cleared quickly when treatment was stopped.

Meprobamate

Allergic reactions constitute the most serious complication of meprobamate therapy. The most often reported reaction is an episode of chill, fever, vascular collapse, gastrointestinal symptoms and skin rash following within hours the first or second dose of the drug. The rash has been described as urticarial, petechial, morbilliform, or as simple erythema.[23] It shows a predilection for the pelvic girdle, breast area, axillae and dependent parts. Cases where the rash has a petechial or purpuric quality have been described as nonthrombocytopenic purpura.[24] Platelets are present in normal numbers, the only bleeding abnormality being a positive tourniquet test.

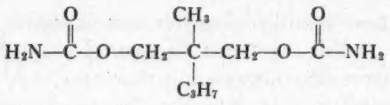
Occasionally these reactions may be delayed, not appearing for from several days to two months after treatment has been started.[25] One case that occurred after eight days of therapy began with purpura and proceeded to an aplastic anemia which was fatal a month later.[26] Cases reported as occurring after two months of treatment have been described as erythema multiforme and have been slow to respond to treatment. Vascular collapse, simulating an anaphylactoid reaction, has been the most alarming symptom. Usually the rash subsides promptly with cessation of the drug or brief use of antihistaminics or adrenocortical hormones.

The challenge test has provided convincing evidence that this reaction to meprobamate is allergic. In almost every instance where challenges have been made, the reaction reappeared almost immediately. In some instances, sensitivity was still present several months after the original reaction. The following case from my experience raises some interesting questions about meprobamate allergy.

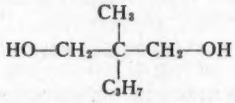
Case 3. The patient was a 62 year old man with a schizophrenic reaction. He had previously received several months of reserpine therapy without signs of drug reaction. Occasional doses of pentobarbital, secobarbital or chloral hydrate had also been given without reactions.

Meprobamate was started on January 8, 1957. After two 400-mg. doses he complained of malaise and had a fever of 101.4° F. An erythematous petechial rash was distributed over the groins, genitalia, and the inner aspects of thighs and arms, wrists and ankles. Meprobamate was stopped, tripelennamine was started, and the rash cleared in the next few days. He received a few doses of phenobarbital during this period.

To test for cross-sensitivity, it was decided to administer a drug similar to meprobamate but lacking the carbamic acid groups (figure 1). On January 21, 1957, the patient received two 250-mg. test doses of this substituted propanediol, and



2-methyl-2-n-propyl-1,3-propanediol dicarbamate
(meprobamate)



2-methyl-2-n-propyl-1,3-propanediol

FIG. 1.

a single 250 mg. test dose on the following day. No reactions were noted. On January 24, 1957, he was started on 250 mg. of this preparation three times daily, and continued to receive it until January 29, 1957, with no adverse reactions. On January 29, 1957, after a single 400-mg. dose of meprobamate, he again developed a rash similar to that noted before but without so much constitutional reaction. Despite resumption of the analogous propanediol drug in doses of 250 mg. three times daily on January 30, 1957, the rash promptly cleared. On February 5, 1957, he received another 400-mg. dose of meprobamate and again developed the characteristic eruption within a few hours.

Subsequently he received challenge doses of several drugs containing the $CONH_2$ groups, such as carbromal, Bromural, ethinamate, another substituted propanediol, and a meprobamate isomer. None of these challenges reproduced the reaction. On April 2, 1957, the patient was again challenged with meprobamate. On this occasion no reaction occurred. The following day he received 800 mg. of drug, and on April 4, 1957, the drug was resumed at a daily dose of 400 mg. three times daily. He was able to take this dose of drug for several months following without additional reaction.

DISCUSSION

If agranulocytosis and jaundice were toxic rather than allergic reactions to chlorpromazine, one should expect a higher incidence with increased doses or prolonged treatment. Actually, both complications occur relatively early in treatment and independently of dosage. The frequent reports of positive challenge tests to chlorpromazine, with rapid appearance of jaundice or signs of impaired liver function, are the strongest evidence for an allergic basis of jaundice. Challenge tests have been performed far less often in patients recovering from agranulocytosis (for obvious reasons), but it does appear that they can be successful. The failure thus far to demonstrate leukocyte agglutinins remains the major objection to an immunologic mechanism for agranulocytosis.

Many phenothiazine derivatives are being introduced into medicine at this time. Alterations of chemical structure, even though slight, might possibly reduce or eliminate the type of sensitivity that produces agranulocytosis or jaundice. Cross-sensitization might also be avoided. Despite

fairly extensive use of proclorperazine and perphenazine, neither jaundice nor agranulocytosis has thus far been reported from either drug. On the other hand, both agranulocytosis and jaundice have been reported from promazine and mepazine, as well as other phenothiazines not widely used. Even now it appears that chlorination of the phenothiazine ring is not the critical determining factor in producing sensitivity.

In evaluation of claims that new phenothiazine derivatives may produce less jaundice or agranulocytosis than chlorpromazine, the time relationships of these complications to treatment should be kept in mind. Statements of prevalence of jaundice can be made with certainty only in cases treated for at least five weeks. In the case of agranulocytosis, at least three months of treatment would be necessary before one could say with certainty that this complication would not have appeared. At present, it does seem that the introduction of the piperazine ring into the structure of these drugs increases the therapeutic potency of these drugs (proclorperazine, perphenazine) and decreases their allergenic potential.

Reserpine barely qualifies as an allergen on the basis of the comparatively rare reports of reactions. It does appear to have the potential of producing immunologic thrombocytopenia, like quinidine, Sedormid, and some sulfonamides. Aggravation of such allergic disorders as chronic urticaria, bronchial asthma or atopic rhinitis might be expected from the parasympathomimetic action of the drug.

Reactions to meprobamate, peculiar in that they may occur with the initial doses of the drug, raise some interesting questions. Experience in the case reported above suggests that the carbamate groups are the determinant factor in meprobamate sensitivity. Perhaps previous sensitization can be produced by other ureide sedatives and hypnotics, including barbiturates, many of which have portions of the molecule resembling the carbamate groups. Such a hypothesis would explain the immediate reaction to meprobamate demonstrated by some patients. Cross-sensitivity between various carbamate-containing compounds was not demonstrable in our case because the patient's sensitivity to meprobamate was lost during these trials.

Summary

Allergic reactions are responsible for some of the most important complications of tranquilizing drug therapy. In two of the three major classes of tranquilizing drugs these reactions are of the greatest importance.

Sensitivity to chlorpromazine may be manifested by agranulocytosis, jaundice, dermatitis and other minor reactions. Strong circumstantial evidence suggests that agranulocytosis from chlorpromazine is of immunologic origin, though this contention remains to be proved. Chlorpromazine jaundice has been reproduced often enough by the challenge test to implicate drug allergy as the mechanism. The relationship of agranulocytosis and jaundice to other phenothiazine drugs is discussed.

Reserpine is of low allergenicity. Occasionally, angioneurotic edema or urticaria has been reported. Two case reports are presented which indicate that purpura may be produced by the drug.

Meprobamate sensitivity is manifested by fever, skin rashes and constitutional signs, including vascular collapse. This sensitivity is peculiar in that it commonly is produced by the initial dose of drug. A case is reported that implies that the carbamate groups of the meprobamate molecule determine this type of sensitivity.

ACKNOWLEDGMENT

Mr. William A. Dunlap performed the serologic tests mentioned in this paper.

SUMMARIO IN INTERLINGUA

Tres classes de drogas tranquillisatori ha essite usate extensemente. Illos es le derivatos de phenothiazina, le alcaloides de Rauwolfia, e substituite propanedioles o butanedioles. Reactiones allergic post le uso de iste drogas ha essite reportate.

Le major reactiones allergic a derivatos de phenothiazina es agranulocytose e jalnessa. Altere reactiones es dermatitis, febre, eosinophilia, purpura nonthrombopenic, e asthma. Agranulocytose ha essite reportate como occurrente post administrationes de chlorpromazina, promazina, e mepazina, sed le incidentia general es extrememente basse. Feminas de etate avantiate es le plus susceptibile de disveloppar iste complication, le qual occurre quasi semper durante le prime 12 septimanas del curso de tractamento. Jalnessa ha essite reportate como occurrente post administrationes de chlorpromazina e mepazina. Il ha essite asserite que promazina causa jalnessa in patientes previemente sensibilisate a chlorpromazina, sed iste typo de sensibilitate cruciate non poteva esser demonstrate in le presente studio. Iste complication—occurrente in minus que 2% del patientes tractate con chlorpromazina—se manifesta characteristicamente durante le prime cinque septimanas del curso de tractamento. Le morbo ha essite reproducite in un satis grande numero de tests aggressori pro suggerer le alte probabilitate que illo es un reaction allergic.

Reserpina e altere alcaloides de Rauwolfia non es particularmente allergene. In le presente studio un caso es reportate que indica que reserpina es capace a causar un subite e mortal purpura. Definite purpura thrombocytopenic se trova reportate in le litteratura german, probabilemente super un base immunologic. Purpura nonthrombopenic de leve grados pote etiam esser producite per reserpina.

Meprobamato produce un reaction que es characterisate per rigor, febre, collapso vascular, symptomas gastrointestinal, e un eruption cutanee que occurre tosto post le prime o secunde dose del droga. In tal patientes, tests aggressori se ha monstrate uniformemente positive. A vices le reaction allergic a meprobamato es retardate e se manifesta solmente post que le droga ha essite in uso depost plure menses. Reactiones del typo de urticaria, purpura, e erythema multiforme ha essite reportate. In le presente studio un caso es reportate in que un derivato de propanediol—completemente simile a meprobamato con le exception del gruppos de acido carbamic—esseva tolerate sin reaction per un patiente sensibilisate. Iste caso suggere le possibilitate que sensibilitate a meprobamato es determinate per le gruppos de acido carbamic.

In le caso del derivatos de phenothiazina, reactiones allergic representa le principal complication del tractamento. Plus recente derivatos de phenothiazina—incorporante le nucleo de piperazina (proclorperazina, perphenazina)—pare haber un augmentate effecto therapeutic e reducite effectos sensibilisatori. Usque al tempore presente, nulle caso de agranulocytose e nulle caso de jalnessa ha essite reportate post le uso del un o del altere del duo drogas mentionate.

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HOMOZYGOUS HEMOGLOBIN C DISEASE: REPORT OF THREE CASES*

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ALTHOUGH hemoglobin electrophoresis is being performed in numerous centers throughout the world, patients with homozygous hemoglobin C disease are encountered infrequently.[1] Hemoglobin C trait has been found to be present in 2 to 3% of American Negroes,[2, 3] and the incidence of homozygous hemoglobin C disease has been calculated to be one in 6,000 Negroes.[1] In the course of a study of hemoglobinopathies during the period of 1953 to 1956, three patients with this hemoglobin pattern have been encountered. Each of these patients was a diagnostic problem until hemoglobin electrophoresis was performed, which revealed only the presence of hemoglobin C. This hemoglobin alone presumably accounted for the various manifestations in each case. These three patients illustrate the clinical features associated with this abnormal hemoglobin type, as well as some variations from the findings reported by others. To amplify the characteristic picture of this disease, it is our purpose to report the clinical details of these three patients. In addition, studies of the families and of ferrokinetics using radioactive iron,[59] as well as red cell survival employing radioactive chromium,[51] will be described.

Homozygous hemoglobin C disease is, in general, characterized by the presence of a mild to moderate chronic hemolytic anemia occurring almost exclusively in Negroes, with constant and sometimes massive splenomegaly, variable degrees of hepatomegaly, occasional fleeting arthralgias, and infrequent low grade icterus. Laboratory features include a mild to moderate anemia which is normochromic and normocytic, low grade reticulocytosis, numerous target cells, decreased osmotic fragility, absence of sickling, normal amounts of fetal hemoglobin, shortened red cell survival and normoblastic hyperplasia of the bone marrow.

Prior to the description of the first case of hemoglobin C disease, these patients presented diagnostic difficulties and some were considered to have thalassemia.[4] As will be brought out, one of our patients, prior to the advent of hemoglobin electrophoresis, was a perplexing problem and was evidently considered to have a potentially fatal disease.

* Received for publication May 29, 1957.

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Current concepts of genetics imply that homozygous hemoglobin C disease results from the inheritance of the gene for hemoglobin C from each parent. Since the patient presumably possesses only genes for hemoglobin C, each of the offspring will possess hemoglobin C together with another hemoglobin carried by a gene inherited from the other progenitor. The resulting clinical pictures in the offspring may vary from the asymptomatic carrier state (AC), without anemia but with a few target cells, to hemoglobin C-thalassemia, or sickle cell hemoglobin C disease, which has a clinical picture distinct from hemoglobin C disease. These clinical states have been described by others.[3, 5, 6, 7, 8, 9] Of course, other as yet undescribed combinations are also possible.

Case Reports

Case 1. A 67 year old Negro woman was admitted to the Orthopedic Service of the City of Detroit Receiving Hospital on July 14, 1956, because of a fractured left hip following a fall. Under spinal anesthesia on July 19, 1956, a Smith-Petersen nail and a Thornton plate were inserted to immobilize the intertrochanteric fracture of the left femur.

Postoperatively, a right lower lobe pneumonia developed. It was also noted that the patient's hemoglobin had fallen from 12 gm. per 100 ml. on admission to 8.7 gm. per 100 ml. on the fourth postoperative day, although blood loss at the time of operation had been minimal. After transfusion of 2,500 ml. of whole blood during the following three weeks, the hemoglobin reached only 10 gm. per 100 ml. Because of the persistent anemia and splenomegaly noted postoperatively, she was transferred to the Medical Service on August 16, 1956.

Further history was obtained at this time. She had known of her abdominal mass (spleen) for as long as she could remember, had never experienced discomfort from it, and had not noted any recent change in its size. She denied ever having been told of anemia or treated for it. She had never received any blood transfusions until the present hospitalization. She also denied jaundice, arthralgia, leg ulcers, myalgia and abdominal pain. She had been treated for hypertension and for symptoms of cardiac failure for the last 10 years. Her review of systems was otherwise negative except for her obstetric history. She had had 11 pregnancies without miscarriages or abortions, and had given birth to 13 living children (all at home except the last), without complications. However, all but one of her 13 children had subsequently died, under uncertain circumstances in most instances, 11 during childhood and one son after reaching adulthood. A daughter, her thirteenth child, is the only surviving member. The patient did not know about the health of her only sibling. Her mother and father had died of "old age."

Physical examination revealed a well developed, well nourished Negro woman in no acute distress. Her height was 162 cm. (vertex to pubis, 72 cm.), and her span was 174 cm. The blood pressure was 120/60 mm. of Hg; pulse, 88 per minute and irregular. The fundi revealed grade II hypertensive changes. There was no significant lymphadenopathy. Dullness and moist râles were present at the right lung base. The heart was enlarged to the anterior axillary line. A grade III, rather harsh apical systolic murmur was transmitted over the entire precordium. The rhythm was grossly irregular. The liver was firm and nontender, and was palpated 4 cm. below the right costal margin. The spleen was lying laterally and was elongated, firm and nontender, and reached 17 cm. below the left costal margin on quiet respiration. Osteoarthritic changes were present in the left knee. There was marked varicosity of the calf veins on the left, with 1 plus pitting edema. A trace of ankle

edema was present on the right. The remainder of the physical examination was not remarkable.

Laboratory examinations revealed the following: hemoglobin ranged from 8.7 to 11.5 gm. per 100 ml.; erythrocytes between 2.96 and 3.82 million per cubic millimeter; hematocrit between 29 and 32 cell vol.%. Reticulocytes ranged from 1.2 to 4.8%; leukocytes were initially elevated up to 23,500 per cubic millimeter, because of pneumonia, but later were around 10,000 per cubic millimeter, with a normal differential except for a slight increase in eosinophils; platelets ranged from 112,000 to 154,000 per cubic millimeter, and the mean corpuscular volume was 85 cubic microns, mean corpuscular hemoglobin, 29 micromicrograms, and mean corpuscular hemoglobin concentration, 34%. Approximately 30% target cells were noted in the peripheral blood smear. The sickle preparation was negative. Hemoglobin electrophoresis revealed only hemoglobin C after the transfused red cells had disappeared (figure 1). Fetal hemoglobin by the alkali denaturation method was 1.2%. The findings on bone marrow aspiration were essentially normal, except for the presence of 4% plasma cells. The serum bilirubin ranged from 5.6 mg. per 100 ml. total, with 2.8 mg. indirect shortly after surgery, to a low of 1.7 mg. total, with 1.3 mg. indirect Mechanical fragility was 10% under oxygen (our normal, 2 to 7%), and 13.8% under 10% carbon dioxide (our normal, less than 10%). Hemolysis of the red cells began in 0.50% saline and was complete in 0.20% saline. No circulating hemolysins or agglutinins were present. The fecal urobilinogen excretion on a four-day collection was 140 mg. per day. The hemolytic index was 29 (normal, 11 to 21). The plasma iron was 83 gamma%, and when repeated in conjunction with the iron studies was 70 gamma%. The Coombs' test was negative. Urine urobilinogen was positive in 1:320 dilution, but was negative for bile. The bromsulfalein test revealed 11% and 4% retention in 45 minutes on two occasions. The serum albumin was 2.9 gm. and globulin 3.5 gm. per 100 ml. initially, but later they were 5.7 and 4.5 gm. per 100 ml., respectively. Thymol turbidity was 4 units. Cephalin-cholesterol flocculation was 3 plus initially, but was negative on repeat. The prothrombin time was 19.8 seconds, with a control of 14.8 seconds. The sputum culture revealed *Micrococcus pyogenes*, var. *aureus*.

Hemoglobin electrophoresis of the patient's daughter revealed the presence of both hemoglobin A and C (figure 1). Further family studies were not possible, since

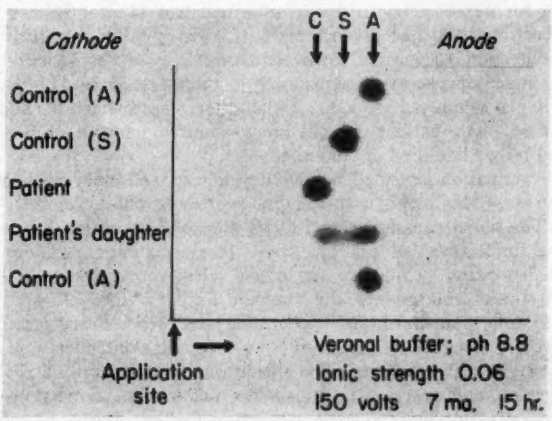

FIG. 1. Hemoglobin patterns by filter paper electrophoresis of case 1 and her daughter.

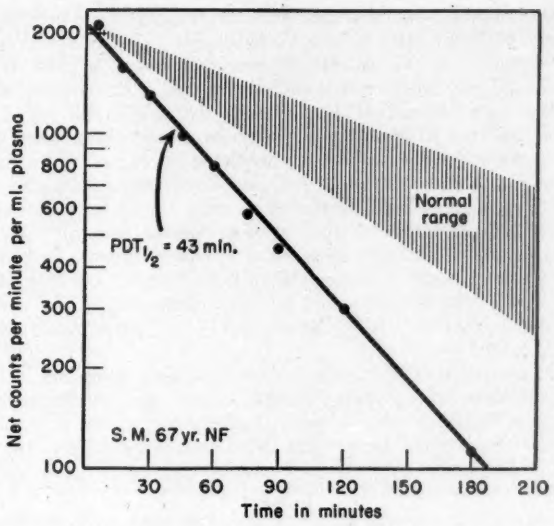

FIG. 2. The rate of disappearance of injected radioactive iron from the plasma in case 1.

the patient's husband, both parents, and 12 of her 13 children were dead, and the whereabouts of her only sibling was unknown. Red blood cell survival of the patient's own cells within her circulation was determined by employing the radioactive chromium method. The radioactive chromium-51 50% red cell survival time was 21 days (our normal, 26 to 40 days). Sites of red cell sequestration were determined by means of an external scintillation counter.[10] The spleen-to-liver ratio was 2.4 to 1. Ferrokinetics were studied by the use of radioactive iron-59.[11] The PDT½ (plasma iron disappearance half-time) was 43 minutes (normal, 70 to 120 minutes) (figure 2).

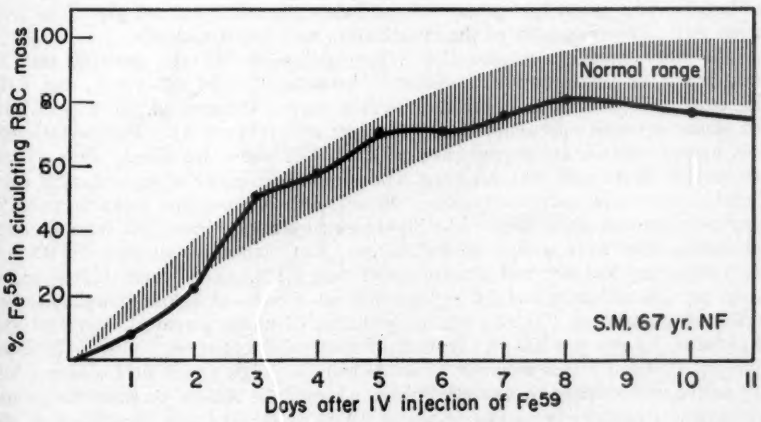

FIG. 3. The appearance of radioactive iron in the circulating red cell mass of case 1.

The incorporation of the injected radioactive iron into red blood cells reached a peak of 81% on the eighth day after injection (figure 3). This is at the lower limit of normal. The remainder of the calculated values are shown in table 1.

Case 2. A 28 year old Negro housewife was admitted to the City of Detroit Receiving Hospital on September 13, 1954, with the chief complaint of jaundice for two days. She had been well until nine days prior to admission, when she had noted the onset of anorexia, followed by nausea, vomiting, fever and chills, dark urine and weakness. She denied previous episodes of jaundice or any arthralgias.

Review of systems disclosed exertional dyspnea for at least the last two years. The patient had been told in 1952 that she was anemic and had been treated with iron. Three pregnancies had been uneventful except for anemia with the last pregnancy. She had felt a swelling in her abdomen for "years," but this had never been painful. She had never been hospitalized previously except for childbirth. Her mother was in good health. The whereabouts of her father was unknown. Two sisters were living and well.

Physical examination revealed a well developed, well nourished, extremely light-skinned Negro woman in no acute distress. There was moderate icterus of the sclerae and skin. The fundi were normal. There was no pallor or significant lymphadenopathy. The lungs were clear. The heart was not enlarged, and no murmurs

TABLE 1

Radioactive Iron Studies

	Patient	Normal
Plasma iron disappearance half-time (minutes)	43	70–120
Fe^{59} utilization by red cells (per cent)	81	83–100
Plasma iron pool (mg.)	2.46	2.4–4.6
Plasma iron turnover rate (mg. per day)	57	32–52
Plasma iron turnover rate (mg./kg./day)	1.06	0.46–0.75
Daily iron pool turnover	23.2	9.6–15.9
RBC iron turnover rate (mg./day)	46	30–50
RBC iron turnover rate (mg./kg./day)	0.86	0.43–0.72
Total red cell iron (mg.)	1954	2450
Red cell iron renewal rate (per cent daily)	2.36	0.97–1.45
Mean red cell life span (days)	42	69–103

were heard. The spleen was palpated 8 cm. below the left costal margin. The liver was not felt. The remainder of the examination was not remarkable.

Laboratory examinations revealed a hemoglobin of 10.3 gm. per 100 ml., 5.8 million red blood cells per cubic millimeter, hematocrit of 34 cell vol.%, and 8,700 white blood cells per cubic millimeter, with a normal differential. The peripheral blood smear revealed approximately 90% target cells (figure 4). Microcytosis and 2 plus hypochromasia, anisocytosis and poikilocytosis were also noted. One normoblast per 100 white cells was present. The mean corpuscular volume was 58 cubic microns; mean corpuscular hemoglobin, 18 micromicrograms, and mean corpuscular hemoglobin concentration, 30%. The bleeding and clotting times, clot retraction and prothrombin time were within normal limits. The platelet count was 250,000 per cubic millimeter, and the reticulocyte count was 2.1%. The serum bilirubin was 8.8 mg. per 100 ml. total, and 3.8 mg. per 100 ml. direct. Alkaline phosphatase was 5.2 Bodansky units per 100 ml.; gamma globulin, 22 units; serum albumin, 4.4 gm., and globulin, 3.1 gm. per 100 ml.; cephalin-cholesterol flocculation, 4 plus in 24 hours. Urinalysis revealed 1 plus albumin, 14 white cells per high power field, positive bile, and positive urobilinogen in 1 to 30 dilution. Hemolytic studies revealed the following: osmotic fragility—hemolysis began in 0.45% saline and was incomplete in distilled water; Coombs' test, negative; sickle preparation, negative; fecal urobilinogen,

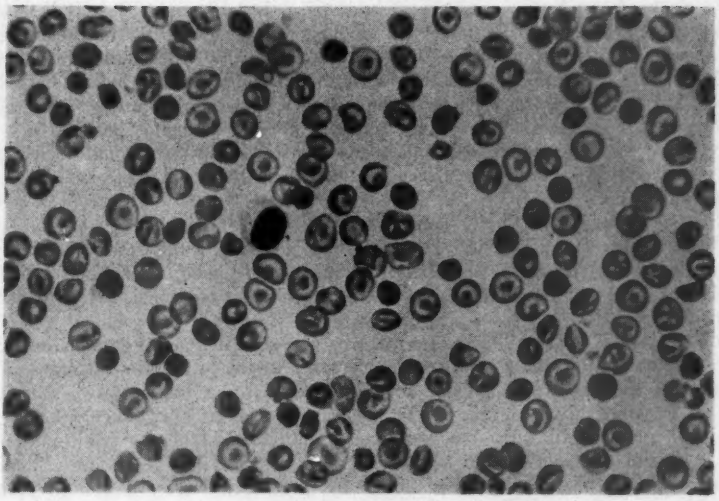

FIG. 4. Peripheral blood smear of case 2. Note the presence of numerous target cells. (600 ×).

291 mg. per 24 hours; hemolytic index, 71; mechanical fragility, 5.1% under oxygen and 12.2% under carbon dioxide; no circulating hemolysins were found. The plasma iron was 142 gamma per 100 ml. The fetal hemoglobin as determined by alkali denaturation was 1.2% (normal). Examination of the bone marrow revealed greatly increased normoblastic erythrocytogenesis, with a myeloid-erythroid ratio of 0.5 to 1. Roentgenologic examinations, including chest, abdomen, bone survey, upper gastrointestinal series and intravenous pyelogram, were not remarkable except for the presence of a very large spleen and slightly enlarged liver.

Course: The initial impression was infectious hepatitis and splenomegaly of undetermined origin. The splenomegaly was adequately explained only after hemo-

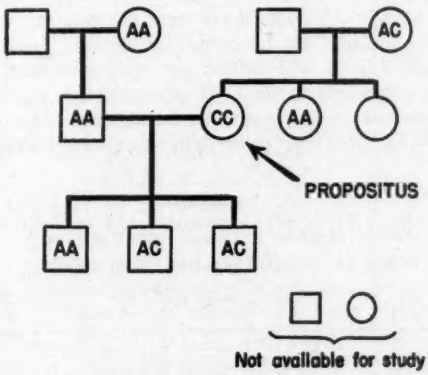

FIG. 5. Hemoglobin types of family members of case 2 as determined by paper electrophoresis.

globin electrophoresis revealed the presence of C hemoglobin. Hemolytic studies, as mentioned above, were consistent with a moderate hemolytic anemia. As the patient's infectious hepatitis improved, the bilirubin gradually fell to normal. Cephalin-cholesterol flocculation, bromsulfalein and alkaline phosphatase have returned to normal, but thymol turbidity has remained slightly elevated (9 units) on follow-up studies. The hemoglobin has ranged between 9.7 and 12.5 gm. per 100 ml., and the reticulocytes have fluctuated from normal to 4.6% during the follow-up period of two and one-half years. The degree of splenomegaly has been unchanged during this period.

Studies of available family members were done. Their hemoglobin types are shown in figure 5. One child revealed only normal hemoglobin. Blood typing (shown in table 2) excluded the possibility of this child's being a true family member. The hemoglobin patterns of the other family members were consistent with current concepts of genetics.

Case 3. A 32 year old Negro woman was first seen in 1947 at another institution with the chief complaint of pressure and a mass in the left upper quadrant of her abdomen of five months' duration. Physical examination was negative except for marked splenomegaly. Significant laboratory studies included: hemoglobin, 10.5 to 11 gm. per 100 ml.; white blood cell count, 11,000 to 12,000 per cubic millimeter, with a normal differential; red cell count, 4.1 to 4.5 million per cubic millimeter; platelet count of 160,000 per cubic millimeter; markedly decreased osmotic fragility (beginning hemolysis at 0.36% saline and incomplete in distilled water). The reticulocyte count was 0.1%. The icteric index ranged from 13.5 to 17 units. There was no sickling. Examination of the bone marrow revealed increased erythrocytogenesis. Chest x-ray was interpreted as "peribronchitis." The patient was discharged with the diagnosis of splenomegaly of undetermined origin, and was told that she had "six months to live."

She was first seen at the City of Detroit Receiving Hospital in March, 1954, when she was admitted with the chief complaint of intermittent "cramplike" pain in the left upper quadrant of her abdomen, occurring in bouts lasting from three or four days to six weeks. There had never been any symptoms of anemia, and no jaundice had been noted. She denied hemorrhages, liver disease and chronic alcoholism.

Physical examination revealed a well developed, well nourished Negro woman who did not appear ill. There was no icterus. The heart and lungs were normal. The liver was palpated 3 cm. below the right costal margin and the spleen 8 cm. below the left costal margin. No leg ulcers were present.

Laboratory studies included the following: hemoglobin, from 10 to 11.6 gm. per 100 ml.; red cell count, 3.68 to 5.35 million per cubic millimeter; hematocrit, 36 to 40.5 cell vol.%; mean corpuscular volume, 93 cubic microns; mean corpuscular hemoglobin, 27 micromicrograms; mean corpuscular hemoglobin concentration, 28%; white blood cell count, 7,000 to 12,900 per cubic millimeter, with normal differential; 22%

TABLE 2

Results of Blood Typing of Family of Case 2
(Child 1 is excluded as a true family member)

	M	Anti-A	Anti-B	A Cells	B Cells	Blood Type
Mother	−	−	−	+	+	AB
Father	−	+	−	−	+	B
Child 1	+	−	+	+	−	A

target cells in the peripheral blood smear; reticulocytes, 0 to 4%; platelets, 73,000 to 193,000 per cubic millimeter; sickle preparation, negative; bleeding and clotting times, normal; bilirubin, 1.8 mg. per 100 ml. total, with less than 0.2 mg. direct. Hemolysis of red cells began in 0.5% saline and was incomplete in 0.2% saline. Mechanical fragility was 5.2% (normal) under oxygen, but 23.2% (increased) under 10% carbon dioxide. Urine urobilinogen was negative. Fecal urobilinogen as determined on a four-day specimen was 463 mg. per 24 hours, with a hemolytic index of 77. Paper electrophoresis revealed the presence of only hemoglobin C. Examination of the bone marrow revealed increased erythrocytogenesis (myeloid-erythroid ratio, 0.6 to 1), with macronormoblasts compatible with hemolytic anemia. Roentgenologic examinations of the bones, chest and gall-bladder were normal except for moderate splenomegaly. The patient failed to return for follow-up.

Discussion

The three patients whose studies comprise the body of this report were all Negro females ranging in age from 28 to 67 years. A summary of the significant features is presented in table 3. Case 1 represents one of the oldest living individuals with this disorder. It appears, therefore, that although hemoglobin C accounts for the mild to moderate hemolytic anemia throughout life, its presence is still compatible with an essentially normal life span. Although fleeting arthralgias have been mentioned previously,[1, 6, 12] none of our patients had this symptom. Only one patient complained of abdominal pain, which was presumably related to the splenomegaly. Marked splenomegaly was present in all three patients, and in our oldest patient, age 67, the spleen was huge. It is of interest that Schwartz's oldest case, age 57, had the largest spleen in his group of patients with homozygous

Table 3

Case	Age	Race	Sex	Arthralgia	Abdominal Pain	Transfusions	Splenomegaly	Hepatomegaly	Anemia	Type of Anemia
S. M.	67	N	F	0	0	0*	17 cm.	+	Mild to moderate	Normochromic normocytic
G. B.	28	N	F	0	0	0	8 cm.	0	Mild	Normochromic microcytic
E. B.	32	N	F	0	+	0	8 cm.	+	Mild	Normochromic normocytic

Case	Hb. Ranges gm./100 ml.	Retic. Ranges %	Hb. Type	Fetal Hb. Per Cent	Osmotic Fragility	Fecal Urobilinogen mg./day	Hemolytic Index	Plasma Iron γ %	Target Cells %	Bone Marrow
S. M.	8.7–11.5	1.2–4.8	C	1.2	Decreased	140	29	83	30	Normal
G. B.	9.7–12.5	2.1–4.6	C	1.2	Decreased	291	71	142	90	Normoblastic hyperplasia M:E 0.5:1
E. B.	10.5–11.5	0.6–4.0	C	—	Decreased	464	77	—	22	Normoblastic hyperplasia M:E 0.6:1

* Only after surgery.

hemoglobin C disease.[13] As others have noted that splenomegaly is not a prominent feature in children,[14, 15] it might be inferred that splenomegaly may progress with advancing age, although this is not an invariable finding.[16, 17, 18] Hepatomegaly was present in two of the cases, and this association with homozygous hemoglobin C disease has been noted previously.[13, 16] Although mild to moderate anemia was presumably present throughout life, in no case was it severe enough to require blood transfusions, except after a surgical procedure in our first case. This patient during her hospital course was observed to have a rapid fall in hemoglobin, accompanied by an increase in bilirubin, and it is likely that she had a hemolytic crisis, perhaps precipitated by the surgical procedure.

Low grade reticulocytosis was present at times in all patients. One patient (case 1) was followed for over four months in the hospital with multiple reticulocyte counts, and in no instance did this value exceed 4.8%. This lack of marked reticulocytosis has been observed by others.[1, 6, 13, 14, 19] In this respect, Diggs et al.[20] reported one case with reticulocyte values ranging from 88 to 94% in the presence of normal hemoglobin values. This patient had had a prior splenectomy, however, and the relationship of the splenectomy to this extreme reticulocytosis is not clear. Intra-erythrocytic crystals were found in the case described by Diggs, and in an additional patient reported by Wheby et al.[17] These authors pointed out that the intra-erythrocytic crystals were noted only after splenectomy. Such crystals were not present in any of our cases, but were not expected, since splenectomy was not performed in any case. Definite hemolysis was demonstrated in all patients by an elevated hemolytic index, and in one patient by decreased erythrocyte survival by means of radioactive chromium-51 tagging of her erythrocytes. This hemolysis was reflected by normoblastic hyperplasia of the bone marrow in two patients. In the patient in whom the bone marrow was normal, it was felt that multiple transfusions and the presence of infection may have depressed erythrocytogenesis. Elevation of bilirubin is an inconstant feature. Values for fetal hemoglobin and plasma iron were normal in the two patients in whom these tests were performed. The presence of numerous target cells is a constant and outstanding morphologic feature of the peripheral blood in this disease and is an important diagnostic clue. Although always increased, the great variability in the percentage of target cells is noteworthy as demonstrated in our patients (22 to 90%), as well as in the reports by others.[13, 21] The osmotic fragility of the erythrocytes is decreased and the mechanical fragility is normal or slightly increased.

With the clinical features just described, it is not difficult to see how such patients could be thought to have thalassemia.[4] This diagnosis per se, however, can be excluded by the finding of only hemoglobin C by paper electrophoresis. More difficult to differentiate, however, is the combination of hemoglobin C and thalassemia. This is an uncommon disorder, only

some six cases having been described to our knowledge.[7, 9, 22, 23] In thalassemia alone, or in combination with hemoglobin C, one would ordinarily expect to find a marked microcytosis [7, 9] and increased plasma iron level.[7] Neither of these was present in our patients. Further, no hemoglobin other than C was detected by paper electrophoresis, although we are aware that no abnormal hemoglobin need be present in thalassemia. Basophilic stippling is present in the erythrocytes of the reported cases of hemoglobin C-thalassemia disease, but none was present in the smears of our patients.[7, 9] In addition, studies of other family members in two patients did not reveal evidence suggestive of thalassemia. For these reasons, hemoglobin C-thalassemia disease seems unlikely in these patients, and all of the clinical manifestations are attributed to the presence of hemoglobin C. In one patient (E. B.) the data available do not permit rigid exclusion of hemoglobin C-thalassemia, but homozygous hemoglobin C disease seems much more probable.

Family studies in two patients are confirmatory of the present genetic theory of transmission of hemoglobin C.[24] In one patient (case 2) we were quite surprised to find only hemoglobin A in her oldest alleged son. Detailed analysis of ABO, Rh, M, N, Duffy and Kell factors revealed that this child could not be a bona fide member of the family. Family data in case 1, though incomplete, are unusual because of the striking mortality among her children, only one of 13 being alive and well. Most of them died during infancy or childhood, often under obscure or unexplained circumstances. We can only speculate that a combination of another abnormal hemoglobin inherited from the father may have contributed to this impressive mortality among the patient's children, since homozygous hemoglobin C disease itself probably does not materially reduce life expectancy.[15, 18] One fact established by these studies, however, is that homozygous hemoglobin C disease apparently does not constitute an obstetric problem.

Red cell survival in other cases of homozygous hemoglobin C disease as studied by radioactive chromium tagging of erythrocytes has indicated a shortened survival time of from 19 to 24 days.[25, 26] In our case 1, red cell survival by a similar technic revealed a slight shortening of erythrocyte survival of 21 days. Our normal Cr^{51} 50% red cell survival is 26 to 40 days. Ferrokinetics utilizing Fe^{59} demonstrated that the plasma disappearance half-time was shortened and that the incorporation of the injected tracer dose into the red blood cells was within the lower limits of normal. Utilization may be higher in this patient when not depressed by the presence of her lung abscess. The spleen-to-liver ratio of 2.4 to 1 suggests that the spleen was sequestering and excessively destroying the erythrocytes. Thrombocytopenia of a mild degree was present in two of our patients. This complication has been described by Wheby,[17] and was ameliorated by splenectomy. Although the case reported by Diggs [20] had an improvement

in hemoglobin values after splenectomy, this is not in accord with the experience of others.[13, 16]

The data presented are generally in keeping with the clinical picture of homozygous hemoglobin C disease as previously described. Though a mild to moderate hemolytic anemia is present throughout life, our oldest patient (age 67 years) indicates that this disease may be relatively asymptomatic and is compatible with an essentially normal life expectancy. Furthermore, data available on one patient over a seven-year period during which no significant change in clinical status occurred attest to the relative stability of the clinical picture. These patients were diagnostic problems before the presence of homozygous hemoglobin C disease was established. One should therefore consider this possibility when confronted with a Negro patient presenting with hepatosplenomegaly and mild hemolytic anemia without sickling, and hemoglobin electrophoresis should be performed.

Summary

Three cases of homozygous hemoglobin C disease are presented. All were Negro females; two were young adults, and the third, age 67, is one of the oldest living patients known to us evincing this disorder. All patients presented a fairly uniform clinical picture consisting of mild but constant hemolytic anemia, periodic episodes of jaundice which cleared spontaneously, variable degrees of hepatomegaly and marked splenomegaly.

The outstanding hematologic characteristics were the presence of numerous target cells in the blood smear, increased osmotic resistance to hypotonic saline, increased fecal urobilinogen excretion, slight but fluctuating icterus, mild reticulocytosis, and bone marrow studies compatible with hemolytic anemia. Hemoglobin electrophoresis in each case revealed a uniform spot characteristic of C hemoglobin. Red blood cell survival studies with radioactive chromium in one patient revealed a 50% red cell survival time of 21 days, and ferrokinetics demonstrated normal utilization of Fe^{59}. The diagnostic problem presented by these cases was eventually resolved by the relation of all the clinical manifestations to the presence solely of hemoglobin C.

Acknowledgment

The authors wish to thank Dr. Gordon B. Myers for his helpful criticism and advice, Dr. Elmer R. Jennings for performing the complete blood typing in case 2, and Miss Zora Kingson, M. T. (A. S. C. P.), for her technical assistance. Dr. Melvin R. Sikov kindly assisted in the performance of the radioisotope studies.

Summario in Interlingua

Es presentate tres casos de hemozygotic morbo a hemoglobina C, incontrate in le curso de un studio de hemoglobinopathias durante le annos ab 1953 usque a 1956. Omne le casos concerneva femininas negre. Duo de istas esseva juvene adultas, e le tertie—con 67 annos de etate—es un del plus vetule patientes vive suffrente de iste disordine in tanto que nos lo sape. Omne le patientes presentava un satis uni-

forme aspecto clinic, consistente de leve sed constante anemia hemolytic, episodios sporadic de jalnessa que se clarificava spontaneemente, varie grados de hepatomegalia, e marcate splenomegalia. In nulle caso esseva le anemia satis sever pro requirer transfusiones de sanguine, excepte post un manovra chirurgic in le plus vetule del patientes.

Le major characteristicas hematologic esseva le presentia de numerose cellulas a oculo de ave in frottis de sanguine peripheric (22 a 90%), augmento del resistentia osmotic a hypotonic solution salin, augmento del excretion fecal de urobilinogeno, leve e fluctuante grados de ictero, leve grados de reticulocytose, e constatationes in le medulla ossee compatibile con anemia hemolytic. Le electrophorese del hemoglobina revelava in omne casos un macula uniforme del genere characteristic de hemoglobina C. Le valores pro hemoglobina fetal e pro le ferro del plasma esseva normal in le duo patientes pro qui illos esseva determinate. Studios con chromo radioactive que esseva executate in un del patientes revelava un leve reduction del superviventia erythrocytic, e studios ferrocinetic demonstrava un utilisation normal de Fe^{59}.

Apparentemente homozygotic morbo a hemoglobina C non constitue un problema obstetric. Studios familial in duo patientes confirmava le currente theorias relative al transmission genetic de hemoglobina C.

Cata un del tres patientes representava un problema diagnostic usque le electrophorese de hemoglobina revelava le presentia de solmente hemoglobina C. Il es probabile que iste hemoglobina sol esseva responsabile pro le varie manifestationes in le tres casos individual. Es discutite le difficultate de differentiar inter morbo a hemoglobina C con thalassemia e homozygotic morbo a hemoglobina C.

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HOST FACTORS IN POLYCYTHEMIA VERA*

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THE occurrence of polycythemia vera predominantly in middle life is well documented. Males seem to be affected more frequently than females, but to an extent that varies widely from one reported series to another. The clinical impression is strong, as quoted in current texts,[1-3] that Negroes are rarely affected and Jews relatively often, but published evidence leaves much to be desired. That for Negroes rests on a single series in 1924, in which one of 34 patients was a Negro! The statistical basis for the presumed high incidence among Jews consists of Türk's [5] five Jewish patients of seven with polycythemia vera in Vienna in 1904; Lucas' [6] minimum of 11 of 123, comprising all cases reported up to 1912 (including Türk's); and 64 of 134 patients from several hospitals in New York City and New Haven, reported by Reznikoff, Foot and Bethea [7] in 1935. Videbaek's [8] series from Denmark in 1950 included no Jews among 125 patients, and Lawrence's [9] from California showed "no preponderance of any particular nationality or geographic or religious group." However, the two last-mentioned studies lacked control data.

Clinical impressions may or may not survive statistical test. Thus, MacMahon and Koller [10a] have recently confirmed the impression they attribute to New York City hematologists of the high incidence of leukemia among Jews. On the other hand, they could not substantiate the reportedly low incidence of leukemia among Negroes. Their epidemiologic study was based on data from numerous sources and of varying reliability, such as records from many hospitals and cemeteries, death certificates and other municipal records, and the Federal census. In an attempt to ascertain the incidence of polycythemia among Jews and Negroes, the present investigation has utilized records from a single institution, where adequate controls are available. In the course of this study, several other host factors have been analyzed, including age, sex, blood group, physique, age at menarche and menopause, and associated diseases. One of the youngest cases of polycythemia vera on record has come to light, and additional evidence has

* Received for publication August 30, 1957.
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been obtained relating polycythemia to uterine myoma and to hypernephroma.

Subjects and Criteria

The subjects included all cases of polycythemia vera, 197 in number, admitted to the Presbyterian Hospital ward and private services or seen in its clinic during the 20 years from 1937 to 1957. Since several patients had had their disease for some years, the present series is not restricted to new cases and hence does not afford a basis for estimating incidence of the disease. Ward or clinic patients numbered 123; private patients, 74. No patient was included whose polycythemia could be attributed to known cause, such as cardiopulmonary, endocrine or neoplastic disease, or to physicochemical exposure. Criteria for the diagnosis included elevation of hemoglobin above 18 gm. per 100 c.c., red blood cells above 6.3 million per cubic millimeter, and hematocrit above 55%. Any two or more of these criteria were acceptable, but if only one was available, at least two abnormal determinations were required. Splenomegaly, leukocytosis and thrombocytosis were considered to be confirmatory when present, but were not necessary for the diagnosis.

Control groups will be described in the appropriate sections.

Of special interest were nine patients, seven men and two women, with polycythemia and hypernephroma. They have not been included in our present tabulations. One of the men has shown complete hematologic remission following nephrectomy for two years, and another for 11 years. Two additional patients, a man and a woman, probably had the same combination of diseases, but since the diagnosis of hypernephroma was not so well founded as in the other cases they are included in our tabulations. The association of polycythemia and hypernephroma will be further discussed below, and our cases will be reported in detail elsewhere.[10b]

Results and Discussion

Sex Incidence: Although males predominate in most published series, the sex ratio, male: female, varies from as high as 25:7[4] and 38:14,[11] through intermediate values of 89:51[6] and 78:46,[12] to virtual equality—33:27[13] and 14:16.[14] Some recent series from France[15,16] show 80:65, from Denmark,[8] 74:51, and from California,[9] 57:43.

In the Presbyterian Hospital series, there were 132 men and 65 women, close to a 2:1 ratio. The sexes did not differ in age of onset of the disease, and figures being $53.3 \pm$ s.e. 1.1 years for men, and 54.4 ± 1.6 years for women. Nor did the sex ratio differ among various ancestral groups, the X^2 test giving a p-value of 0.25 for this association.

Age: The average age of onset was 53.7 years, which agrees closely with all previous findings. Videbaek[8] alone has suggested that women may develop the disease earlier than men, since 19% of his female patients

TABLE 1

Polycythemia Vera
Age of Onset

Age in Years	Males		Females		Total	
	No.	%	No.	%	No.	%
0– 9	1	1			1	0.5
10–19						
20–29	5	4	2	3	7	4
30–39	13	10	8	12	21	10
40–49	28	21	10	15	38	19
50–59	40	30	23	35	63	32
60–69	39	30	16	25	55	28
70–79	6	5	6	9	12	6
Total	132	101	65	99	197	99.5
Mean ± s.e.	53.3 ± 1.1		54.4 ± 1.6		53.6 ± 0.9	

but only 5% of his males had their onset before the age of 40. While these percentages differ at the 2% level, neither his mean ages—55 for men, 51 for women—nor the age distributions as a whole differ significantly, and it is statistically unsound to compare extremes of two distributions when the latter themselves do not differ.[17]

In the Presbyterian Hospital series there was no sex difference in average age of onset, age distribution, or percentage of onset before age 40. Age of onset was unrelated to ancestry ($p = .07$). The age distribution is shown in table 1.

One patient whose disease was first diagnosed at age 9 merits presentation as one of the earliest cases on record of polycythemia apparently primary and unaccompanied by congenital anomalies. This patient has led an active life without therapy or complications of his disease for 15 years following diagnosis.

CASE REPORT

A nine year nine month old boy of Italian parentage was first seen in April, 1942, for compound fractures of the radius and ulna, sustained accidentally. After a normal gestation and breech delivery, he weighed six pounds at birth. His infancy and subsequent development were completely normal, and his school work was satisfactory. Except for measles, he had had no childhood diseases, and his exercise tolerance was normal. His father, aged 50, mother (45), three sisters (19, 18 and 14), and a brother (three) were all well, and there was no family history of significant disease. On physical examination his systolic blood pressure was 110 mm. Hg, the spleen tip and liver edge were just palpable, and heart and lungs were normal, as was the remainder of the examination. Six hemoglobin values ranged from 17.4 to 22.6 gm.%, a single red blood cell count was 6.6 million per cubic millimeter, and a single hematocrit was 67.3%. Platelets and red blood cell morphology appeared normal on smear. Several white blood cell counts during sulfadiazine administration varied between 6,000 and 10,000 per cubic millimeter, with normal differential counts. The Kline test was negative, as were urinalysis and abdominal x-rays. His fractures healed after open reduction, and he was discharged in three weeks.

Seven months later the patient was again engaging in full childhood activities, including strenuous exercise. Twenty-eight months later, in August, 1944, he was re-admitted for operative excision of an ulnar scar and resection of the ulnar head, to increase forearm rotation. He was then 12 years old, and had been otherwise perfectly well in the interval. Physical examination disclosed a plethoric appearance, but was otherwise within normal limits. Blood pressure was 104/60 mm. Hg; liver, spleen and kidneys were not felt by four observers. Hemoglobin values varied between 20 and 22.5 gm.%, red blood cells between 8.2 and 9.0 million, and white cells between 6,200 and 6,800 per cubic millimeter. Hematocrit was 70.4%, and red cell morphology was normal. Two urinalyses were negative, while a third showed albumin and occasional white blood cells. Electrocardiogram and chest x-rays were normal. After operation and a few weeks' convalescence he was discharged.

The patient's third admission was in September, 1944, for evaluation of polycythemia. He was then 12 years and two months old, 57 inches tall, and weighed 72 pounds. Physical examination was unchanged, as were hematologic data, urinalysis, chest x-ray and electrocardiogram. Serum proteins were 6.6 gm.%; circulation time, arm-to-tongue, 9.3 seconds, and arm-to-lung, 4 seconds. Unfortunately, his parents refused permission for bone marrow and arterial oxygen saturation studies. When last seen, in 1950, the patient was working full time loading trucks and had no symptoms. In 1957, still asymptomatic, he married.[17b]

Comment: This patient's polycythemia, diagnosed at age nine and conceivably present earlier, was apparently primary, although no definitive documentation was obtained from bone marrow or arterial oxygen studies. Cardiovascular, endocrine, neoplastic or physicochemical causes for the polycythemia were reasonably well excluded. Although the patient was of Italian descent, his elevated hemoglobin levels and normal erythrocyte morphology are incompatible with thalassemia, which has been implicated in some cases of juvenile polycythemia. The absence of leukocytosis, thrombocytosis and splenomegaly can occur in polycythemia vera and, in fact, has characterized several reported cases [18, 19] of heredofamilial polycythemia occurring in childhood.

Hottinger [20] has divided cases of idiopathic polycythemia in the first decade of life into two types: the familial, in which other members of the family are affected,[18, 19] and the sporadic case associated with other anomalies.[21] Our patient certainly does not fall into the latter category, and although the hematologic status of his relatives is uncertain, the good health and normal activities enjoyed by his parents and four siblings make unlikely any serious familial blood disorder.

Ancestry: Brief mention has been made of the single report [4] that polycythemia vera is rare among Negroes. The only other mention of Negroes we have encountered is by Erf,[22] whose 40 selected patients from Philadelphia included two Negroes. Not only was his sample not random, but also the incidence of Negroes in his general population was not given.

The Presbyterian Hospital series included 190 whites and seven Negroes (three men and four women). The Negro polycythemic percentage of 3.6% is very significantly lower ($p < .001$) than that in the hospital population as a whole.[23] This latter figure, 16.4%, is based on all patients,

2,259 in number, who received blood transfusions in this hospital during the first six months of 1953, and may actually understate the proportion of Negroes among clinic as well as bed patients. (Based on numerous "spot checks" over many years, hospital authorities estimate that Negroes comprise about 25% of all Presbyterian Hospital and clinic patients.) Only one Negro patient, a male, was hospitalized for symptoms referable to his polycythemia, the diagnosis being discovered incidentally in the others, and in no case was the disease severe or attended by serious complication. Of the two women who received pelvic examination, both had fibroids, an association of occasional etiologic significance, as will be discussed. Thus, polycythemia vera is indeed rare and, if one may generalize from such small numbers, apparently mild among Negroes. In this connection, it may be noted that of Erf's [22] two Negro patients in a selected sample of 40 primary polycythemics from Philadelphia, one, a male, had an initial red cell count of only 6 million per cubic millimeter, and the other, a woman, lacked leukocytosis.

As for the common notion that Jews are particularly prone to polycythemia vera, the published evidence has been briefly noted above. The fact that two of Osler's [24] four patients were Jews is of historical interest but little else. Of the five additional cases Osler had collected from the previous literature, none was Jewish. With very small numbers and without controls, Türk's [5] figure of five Jewish patients out of seven hardly proves the point. Lucas' [6] figure of 11 known Jews among 123 cases reported to the year 1912 means little, since information on race or religion was available for only 20 patients. One can merely guess whether the true proportion would be closer to 11 : 20 or 11 : 123—and neither ratio would mean much unless the incidence of Jews in the population at risk were known. As Dameshek and Henstell [25] pointed out, the fact that their own 20 patients were all Jews may reflect merely the fact that they were drawn from the predominantly Jewish population of the Beth Israel Hospital in Boston. These authors had the clinical impression that their patients with polycythemia vera contained a higher Jewish percentage than did those with pernicious anemia from the same hospital, and that in other Boston hospitals polycythemia vera was encountered disproportionately often among Jews. However, they also referred to an unpublished study [26] concluding that, over a 20-year period at the Peter Bent Brigham Hospital in Boston, there was no higher proportion of Jews among patients with this disease than among the total population of the hospital.

The data of Reznikoff,[7, 27] published in 1935 and 1939, afford the strongest evidence that Jews are more prone to polycythemia than are non-Jews. The incidence of Jews born in Eastern Europe was 48% among primary polycythemics from six hospitals, as compared to approximately 9% of the general admissions of those hospitals. The word "approximately" should be emphasized, since in two of the six hospitals there was

no information on race or religion, and Reznikoff considered all patients of Eastern European birth to be Jews; in two other hospitals, the percentage of Jews was "estimated," and in the others it was based on a sample year. For the sample year, Bellevue Hospital was said to have 3% of Jews, whereas actual figures in a 1933 study [28] were 7,700 Jews among 63,000 ward discharges, or 12.2%. (About the same percentage obtains for 1956.) Underestimation of the Jewish incidence in the control group is further suggested by comparing Reznikoff's approximation for five New York City hospitals, 9.2%, with the census figure of 27.2% for New York City in 1930.[29]

A possible explanation for such discrepancies and for the underestimation of the Jewish control percentage is the use of birthplace, which is genetically irrelevant, as a criterion. Since polycythemia vera is a disease of later life, comparison of such patients with a younger group, many American-born and who may even include their own children, will not reflect the true hospital incidence of Jews of Eastern European descent.

But even after allowance is made for all sources of error, the concordance from six hospitals is striking, and Reznikoff's study, the only one in the literature offering any control information, certainly indicates a preponderance among Jews. A more precise definition of this tendency is in order.

Among the present 197 patients with polycythemia vera, 65 were Jewish, a proportion of 33.0% of all and 34.2% of the 190 white patients. These percentages are significantly greater ($p \leqq .001$) than those for the Presbyterian Hospital "transfusion group," where the 364 Jews comprised 16.1% of all 2,259 patients, and 19.7% of 1,848 white patients. The Jewish incidence in the "transfusion group" resembles that derived from a separate compilation by the Chaplain's office, which reports the percentage of Jewish admissions as ranging between 18% and 20% for each of the four years from 1952 to 1955. Virtually all the Jews were of Central or Eastern European descent. (Reznikoff gave a similar figure of 15% for the Presbyterian Hospital in 1935.)

It may thus be concluded that the incidence of polycythemia vera is indeed higher among Jews than expected, but by more nearly a 2:1 ratio than the 5:1 ratio usually quoted. This increased Jewish susceptibility parallels that reported by MacMahon and Koller [10] for leukemia.

As for other ancestral groups, the number and percentages of those with polycythemia vera were as follows: "Old American" * and British, 46 (24%); German, 22 (11%); Irish, 20 (10%); Mediterranean and French, 15 (7.5%); Levant and Near East, seven (3.5%); Scandinavian, four (2%); Central European and Slavic, three (1.5%); Puerto Rican, two (1%); other Latin American, two (1%); and Chinese, one (0.5%).

* One whose four grandparents were born in the United States.

These percentages did not differ from the corresponding ones for the hospital population as a whole.

Physique: Clinical impressions unsupported by data but currently quoted [1] have been advanced by Weber,[30] Zadek [31] and Harrop [32] that patients with polycythemia vera tend to be slender. Hirvonen [33] reported, however, that, among Finnish patients, normal, "somewhat strong" or "powerful" builds predominated among 24 certain and 10 uncertain primary polycythemics, as did normal height-for-weight among 18 certain and six uncertain cases. According to Weber, patients with the hypertensive polycythemia of Gaisböck are mostly slender, whereas Zadek characterized them as stocky. No appropriate studies have been made.

Of the Presbyterian Hospital patients with polycythemia vera, weights were obtained for 120 white men and 59 white women. Weight loss of 10 pounds or more was reported by 32 of the men (21 concomitant with polycythemia, 11 for other reasons), and 18 of the women (12 with onset of polycythemia, six for other reasons), for whom weight was taken as the average adult value, not necessarily the maximum ever attained. Height and the height/$\sqrt[3]{\text{weight}}$ index, a measure of body build, were obtained for fewer patients, as shown in table 2.

As a comparison for the polycythemic women, 139 white women have been drawn from various Presbyterian Hospital outpatient clinics, chiefly

TABLE 2

Physique in White Patients With Polycythemia Vera and in Persons Without Known Disease

	Men						
	Polycythemia Vera (Presbyterian Hospital)			Normal Canadians*			Difference
	No.	Mean ± s.e.		No.	Mean		
Age (yrs.)	120	53.3	1.1	ca. 3,000	ca. 53		
Height (in.)	39	67.7	0.5		66.6		?
Weight (lbs.)	120	166.2	2.5		162.0		n.s.†
Height/$\sqrt[3]{\text{Weight}}$	39	12.4	0.12		12.2		n.s.
	Women—Presbyterian Hospital						
	Polycythemia Vera			Without Disease			Difference
	No.	Mean ± s.e.		No.	Mean ± s.e.		
Age (yrs.)	59	54.4	1.6	139	46.2	1.1	
Height (in.)	25	63.9	0.5	139	62.6	0.2	$p < .02$
Weight (lbs.)	59	145.3	3.0	85‡	142.2	2.3	n.s.
Height/$\sqrt[3]{\text{Weight}}$	24	11.8	0.16	85‡	12.1	0.09	n.s.

* See text.
† Not significant.
‡ Excludes 54 women with more than a five-pound loss from average adult to current weight.

medical, dermatologic and gynecologic. By history, examination and later course these women proved to have, or to have had in the past, no known disease other than childhood or certain infectious diseases. Tuberculosis and poliomyelitis were disqualifications, as were all major disease entities, and even such conditions as labile or minimal hypertension, fibroids, neurodermatitis, seborrhea and "psychoneurosis." These women were roughly similar in ancestry to the polycythemics but of somewhat lower social status, since 30% of the polycythemic women were private patients. All 139 "normal" women were used in computing height, but for weight and the height/ $\sqrt[3]{\text{weight}}$ index, only those were included who had never weighed more than five pounds above their current weight.

TABLE 3

Physique in White Patients With Polycythemia Vera, With and Without Hypertension

	Men						
	Without Hypertension			With Hypertension			Difference ($P <$)
	No.	Mean	± s.e.	No.	Mean	± s.e.	
Height (in.)	30	68.3	0.6	9	65.6	0.7	.02
Weight (lbs.)	84	163	3	34	172	4	.07
Height/$\sqrt[3]{\text{Weight}}$	30	12.6	0.14	9	11.9	0.17	.002
	Women						
	Without Hypertension			With Hypertension			Difference
	No.	Mean	± s.e.	No.	Mean	± s.e.	
Height (in.)	16	63.8	0.7	9	64.1	0.7	n.s.*
Weight (lbs.)	40	146	3	19	144	6	n.s.
Height/$\sqrt[3]{\text{Weight}}$	16	11.9	0.2	8	11.7	0.3	n.s.

* Not significant.

Unfortunately, no comparable series of "normal" Presbyterian Hospital men is available. In the absence of adequate controls, the best substitute we have found consists of Canadian men measured during a national survey [34] in 1953. Canadian women from the same source approximate Presbyterian Hospital women so closely in the middle decades that we have assumed—perhaps erroneously—that the same holds true for men. The data have been weighted to conform to the age distribution of Presbyterian Hospital polycythemic men.

Table 2 shows that the male polycythemics were somewhat taller, possibly significantly so, than Canadian men, but no different in weight or body build. Among Presbyterian Hospital white women, the polycythemics were taller (of borderline statistical significance) but no heavier and no

different in body build from the "normal" comparison group. These minimal physical differences between polycythemics and control subjects are more likely to be sampling accidents than associations with the disease.

In summary, no convincing evidence has been found to support the impression that polycythemics tend to be of slender or other distinctive build.

As for patients with polycythemia and hypertension, the so-called Gaisböck's syndrome (unlike Gaisböck's, however, our group includes those with splenomegaly), table 3 compares their physique with that of polycythemics without hypertension. The men with Gaisböck's syndrome were indeed of stockier build, but the subjects are few in number. The women showed no significant physical difference. Before any practical, as opposed to statistical, significance can be attached to these findings, more data are needed.

Blood Groups: The distribution of ABO blood groups has been studied in a wide variety of disorders, but not as yet in polycythemia vera. Table 4 compares the distribution among 55 white patients with the disease and

TABLE 4

ABO Blood Groups in White Patients Receiving Blood Transfusion and Those With Polycythemia Vera

	Blood Group								Total No.
	O		A		B		AB		
	No.	%	No.	%	No.	%	No.	%	
Polycythemia Vera	21	38.2	27	49.1	5	9.1	2	3.6	55
"Transfusion Group"	802	43.4	751	40.6	213	11.5	82	4.4	1,848

1,848 white patients in the Presbyterian Hospital "transfusion group" already mentioned. There was no difference, the X^2 test giving a p-value of 0.37.

Age at Menarche and Menopause: Attempts have been made to relate these constitutional traits to disease, especially breast [35, 36] and uterine [37, 38] cancer, but not as yet to any blood disorders. Thirty-five white women with polycythemia vera reported menarche at $14.0 \pm$ s.e. 0.3 years, which did not differ at all from menarcheal age in two other series of white women from the Presbyterian Hospital. For 50 women in the "normal" comparison group, the figure was 14.0 ± 0.2 years, and among 223 normal pregnant women, it was 13.85 ± 0.1 years.

Natural menopause occurred among 37 white women with polycythemia vera (not necessarily the same patients included above for menarche) at a mean age of 49.0 ± 0.65 years. This did not differ significantly from that of 47.8 ± 1.5 years for 12 "normal" women, much too small a control group, or from the figure of 50 years for each of two published series [39] of

New York City women, 160 Italians and 117 Jews. Sixty-one healthy women from another New York City clinic, reasonably similar in ancestry to the polycythemics but higher in economic status, had a menopausal age of 50.0 ± 0.4 years (unpublished data).

Association with Other Diseases: As with all host factors, tabulating the coincidence, or lack of it, of various diseases is far from idle enumeration. Knowledge of the magnitude of association can complement the case study in directing attention to avenues of research into the mechanisms involved. For example, observation of the relative rarity of thyrotoxicosis in association with cancer has stimulated much basic investigation.[40] Awareness of the increased incidence of gout in polycythemia vera has been a factor leading to studies in purine metabolism and the concept of secondary gout.[41] The occasional association of polycythemia with brain tumor,[42-45] particularly subtentorial and vascular ones, with uterine myomas [46-50] and with hypernephroma [51-53] has been repeatedly documented, as have some cases of hematologic remission following removal of each type of tumor. Tabulation of the incidence of these and other disorders in patients with polycythemia may disclose additional etiologic factors, clarify the nature of primary polycythemia, and indicate new directions for research into the mechanisms of erythropoiesis.

Disorders coexisting with polycythemia can be grouped under two headings: those known to be associated, etiologically, or as part of the disease, or as a complication, and those not so recognized at present. Table 5 presents both groups, the former with comparative figures for three other large series. The incidence of such conditions as hypertension, arteriosclerosis, peptic ulcer, vascular thromboses, gout and cirrhosis of the liver [13] parallels general experience. No case of multiple myeloma was encountered in our series, or in those of Videbaek [8] or the Mayo Clinic group, though Lawrence [9] has observed four and quoted three from the literature. As regards leukemia, myeloid metaplasia and myelofibrosis, our combined total of 7.6% is insignificantly less ($p > .10$) than the 12% reported by Lawrence.[58] Of our 15 patients with these bone marrow dyscrasias 10 had had previous radiotherapy, whereas Lawrence found an equal incidence in patients with and without previous radiation.

Of the other neoplasms known to be associated with polycythemia, the incidence of *uterine fibroids* among polycythemic women has been reported [49] as two in nine, or 22%, and the incidence of polycythemia among women with fibroids as two in 200, or 1%. Among 39 polycythemic women in the present series with adequate history or pelvic examination, 13, or 33.3%, had had fibroids at some time, a proportion expected from current textbook estimates (20 to 40%) of the incidence of fibroids in the general population. These 13 patients included 11 white women and two Negroes, of whom seven white women and one Negro had had hysterectomy for fibroids years before polycythemia appeared. Of the five remaining cases,

TABLE 5

Diseases, Current or Previous, in 197 Patients With Polycythemia Vera

A. Diseases Known to Be Associated

	This Study	Mayo Clinic[44-57]	Videbaek[3]	Lawrence[9,58]
Number of patients	197	100–163	125	159
Percentages with				
Hypertension	32	19	31	33
Arteriosclerosis	30	27	27	
Myocardial infarction	(6.5)	(5)	(1)	(4)
Uterine fibroids	33*			
Ulcer, peptic	14.5	15	23	13
Duodenal	(13)		(16)	(11)
Gastric	(1.5)		(7)	(2)
Thromboses, extremities	9.5	7	12	17
Venous	(7)			(13)
Arterial	(2.5)			(4)
Myeloid disorders	7.6		2.6	12
Leukemia	(5.6)			
Myeloid metaplasia / Myelofibrosis	(2)			
Cerebrovascular accident	5.5	6, 17	20	10
Gout	5.5	5	9	7
Hypernephroma	4.4†		1.6	1.3
Gastroduodenitis	3.5			
Cirrhosis of liver	1.5	3		1.9
Cerebellar hemangioblastoma	1‡			
Meningioma, sphenoid ridge	0.5§			
Erythromelalgia	0.5			
Raynaud's disease	0.5			
Thromboangiitis obliterans	0.5			

* Of 39 women with adequate history or pelvic examination.
† Of 205 polycythemics—see text.
‡ Of 199 polycythemics—see text.
§ Of 198 polycythemics—see text.

where both conditions coincided in time, polycythemia began in one instance at age 70, and in two others at age 50 and 58, four years after the menopause, whereas in the six published cases,[46-50] age has ranged from 32 to 48. (Only one [49] was postmenopausal, by two years, and in that instance the myoma had begun to enlarge premenopausally, and the duration of polycythemia was unknown.) In our fourth patient, whose polycythemia began at age 43, fibroids were discovered incidentally at autopsy, at age 55. Our fifth patient warrants detailed presentation.

Case 2. A Scottish-born housewife and hospital employee developed both polycythemia and uterine fibroids at age 39. At age 28, on a single determination, her hemoglobin was 10.8 gm.%, and red blood cells were 3.8 million per cubic millimeter. At 39 her preoperative hemoglobin was 19.2 gm.%; red cells, 5.2 million; white cells, 14,600 per cubic millimeter, with a normal differential count. Liver, spleen and kidneys were not palpable. Three days after simple hysterectomy for multiple large myomata, with minimal blood loss and 500 c.c. of saline infusion, hemoglobin was 17.6 gm.% and red cells were 4.9 million per cubic millimeter. The patient remained well for five years, a blood count at age 44 showing hemoglobin of 14.1 gm.%, but one year later she returned with hemoglobin values between 18.5 and 21.2 gm.%,

hematocrits ranging from 59% to 63%, red blood cells, 6.1 to 7.8 million, white cells 8,800 to 11,900, and a single platelet count of 357,000 per cubic millimeter. Her spleen was palpable 1 cm. below the costal margin. In the ensuing two years she has responded well, both clinically and hematologically, to phlebotomies, but her platelet counts have ranged between 600,000 and 700,000 per cubic millimeter.

Comment: This patient's fibroid-associated polycythemia resembles those cited in several respects, such as the premenopausal onset, large size of myomata, absence of marked leukocytosis or hepatic or splenic enlargement, and hematologic remission after myomectomy. Her subsequent development of polycythemia vera is, however, unique. Only one other patient [49] has been followed for a longer period—eight years postoperatively; the other follow-up periods have been one, six and 22 months. It will be interesting to learn whether any of these "cured" patients eventually develop polycythemia vera or other myeloproliferative disorders.

The mechanism for the association of fibroids with polycythemia remains unknown.

Brain Tumor: Up to 1952, 19 cases of polycythemia secondary to brain tumor had been reported,[42] of which 11 originated from vascular tissue and 12 were subtentorial in location. In 1955 Schmid and French [43] reviewed an additional case of cerebellar hemangioblastoma and added one of their own, while in 1956 three more cases appeared.[44, 45] At least two such cases have been encountered at the Presbyterian Hospital, 1% of 199 polycythemics and 5% of 37 cases of cerebellar hemangioma reported from this institution by Cramer and Kimsey.[59] (These authors reported on four cases of polycythemia, or 9%, among 44 patients with cerebellar hemangioblastoma from two institutions.) Neither patient from the Presbyterian Hospital has been included in the present series of 197 polycythemics, nor has a Negro male with polycythemia and middle fossa meningioma, but a white male with probable frontoparietal lobe tumor has been retained.

Hypernephroma: The earliest case, to our knowledge, of hypernephroma coexisting with polycythemia was listed by Bliss [60a] in 1929. Since the cases of Medvei [60b] and Fairley,[60c] Moe [52] has reviewed 10 more, including one of his own, Chwalla [61a] has mentioned another, Berger and Sinkoff [53] five more, and Herbeuval [61b] one, for a total of 20. Our own nine patients from the Presbyterian Hospital, plus one from another institution, all of whom will be fully presented elsewhere,[10b] make the total 30. As with many other diseases, the true incidence of this association will doubtless rise once awareness of the syndrome and its occasional etiologic significance, first discussed by Forssell [62] in 1946, becomes widespread.

Our nine cases from the Presbyterian Hospital occurred among 205 polycythemics, giving a percentage of 4.4% as compared to 1.3% reported by Lawrence and 1.6% by Videbaek. The nine cases comprised 2.6% of some 350 instances of hypernephroma at the Presbyterian Hospital between 1929 and 1957,[63] a percentage similar to the 1.8% reported by Berger and

Sinkoff [53] among 273 cases of hypernephroma. The appreciable coincidence of the two diseases indicates the necessity for urologic investigation of hematuria in patients with polycythemia. The assumption that hematuria is a benign manifestation of the polycythemic process may be a serious error.

As with uterine fibroids and cerebellar hemangioblastoma, the mechanism of polycythemia secondary to hypernephroma is unknown. Other cases of renal involvement in polycythemia include Kurrle's [64a] remarkable patient, who developed polycythemia and hypertension without splenomegaly, concurrently with polycystic renal disease progressing to the point where little if any kidney tissue was detectable at autopsy. Polycythemia has accompanied benign renal adenoma [64b] and hydronephrosis,[64c] disappearing in both cases after nephrectomy. We have observed in another institution a patient with a congenitally absent right kidney who was found to have polycythemia and hypertension, again without splenomegaly, when tuberculosis was discovered in his remaining kidney at age 38. After chemotherapeutic remission of his tuberculosis, polycythemia has persisted, well controlled by phle-

TABLE 5—*Continued*

Diseases, Current or Previous, in 197 Patients With Polycythemia Vera

B. Diseases Not Known to Be Associated

Benign prostatic hypertrophy	24*%
Cholecystitis and cholelithiasis	15.5
Osteoarthritis	9.5
Cancer	7
Skin	(2)
Lung	(1)
Rectum, colon	(1)
Stomach, breast, prostate, brain, Hodgkin's, lymphosarcoma (each)	(0.5)
Sinusitis	6
Emphysema	4.5
Hernia	4.5
Renal calculi	4
Nontoxic nodular goiter	3.5
Chronic cystic mastitis	3†
Fibroma, breast	3†
Ovarian cyst	2.5‡
Tuberculosis	2.5
Migraine	2
Chronic glomerulonephritis	1.5
Rheumatic fever (old)	1.5
Rheumatoid arthritis	1.5
Bursitis	1
Depression	1
Hysteria	1
Parkinsonism	1
Toxic diffuse goiter (old)	1
Argyria, asthma, Epilepsy, hemochromatosis, Paget's, pancreatitis, Poliomyelitis, psoriasis, Retrobulbar neuritis (each)	0.5

* Of 132 men.
† Of 65 women.
‡ One patient of 39 women with adequate history or pelvic examination.

botomy, for eight years since the original diagnosis. The work of Jacobson and associates [65] on the renal production of an erythropoietic factor, if confirmed, may afford a clue to such puzzling cases, as well as to the occasional remission of polycythemia following removal of a hypernephroma.

Diseases Not Known to Be Associated: Most of the percentages in table 5B might be expected from the prevalence of such conditions in the general population. *Tuberculosis* occurred among 2.5% of the present 197 patients with polycythemia vera, and in 3% of 76 deceased patients with polycythemia reported by Videbaek.[8] Some 36 cases have been reported with erythrocyte counts over 5 million, presumably secondary to splenic tuberculosis.[66] However, splenectomy in five such cases was not followed by hematologic remission, and Ellman and Fairburn [67] considered the association fortuitous.

The incidence of biliary and renal calculi (19.5%) was similar to that encountered by Videbaek (18%), but the proportions were reversed in the two series, being 15.5% biliary to 4% renal in the present study, and 7% and 11%, respectively, in Videbaek's group. Such values are not remarkably high in view of the estimated incidence in the general population of gall-stones (at least 10%) [68] and of kidney stones (4 to 5%).[69, 70]

Summary

Among 197 patients with polycythemia vera, 132 were men and 65 women. The average age of onset, which did not differ as between the sexes or among various ancestral groups, was 53.7 years. A case occurring in one of the youngest patients on record, a nine year and nine month old boy, was presented.

Significantly fewer Negroes (3.6%) had the disease than their percentage in the Presbyterian Hospital (16.4), and significantly more Jews (33%) than their hospital percentage (16 to 19). Both of these findings confirm previous impressions, but the Jewish preponderance was about 2:1, less than that usually quoted (4 or 5:1) Among the Negroes, the disease tended to be mild. Polycythemia vera occurred among white ancestral groups other than Jewish with the frequency expected from their hospital distribution.

Contrary to the impression of some that patients with polycythemia vera tend to be slender in build, no real difference was found between such patients and normal controls in height, weight, or height/$\sqrt[3]{\text{weight}}$ ratio. Men (but not women) with polycythemia vera and hypertension were stockier than were those without hypertension, but the number of subjects was small.

In ABO blood-group frequency, age at menarche, and age at menopause, patients with polycythemia vera did not differ from comparison series from the same institution.

Other disorders and complicating illnesses coexisted with polycythemia vera in approximately the proportions previously reported; these condi-

tions included hypertension (32%), arteriosclerosis (30%), peptic ulcer (14.5%), thromboses of extremities (9.5%), myeloid dyscrasias (7.6%), and gout (5.5%). Ten of the 15 patients with myeloid dyscrasias had had previous radiotherapy.

Uterine fibroids occurred in 33% of 39 women with adequate history or pelvic examination. A unique case was presented of polycythemia developing coincident with fibroids, disappearing after hysterectomy, and recurring as polycythemia vera five years later.

Hypernephroma was encountered in nine patients (4.4% of 205 polycythemics). Two of these patients have had complete hematologic remissions following nephrectomy for two and 11 years, respectively, to date. The indication for urologic investigation of hematuria in polycythemia vera was noted.

Summario in Interlingua

Ben que il ha un forte impression clinic que polycythemia ver es particularmente prevalente in judeos e rar in negros, non plus que un sol studio a controlo ha previemente essite effectuate pro cata un del duo gruppos. Inter 197 patientes con iste morbo qui esseva vidite al Hospital Presbyterian in New York City, le procentage del negros (3,6) esseva significativemente plus basse que le procentage del negros inter omne le patientes del hospital (16,4) durante que le procentage del judeos in ille gruppo (33) esseva significativemente plus alte que lor procentage in le population total del hospital (16 a 19). Le preponderantia judee, 2 a 1, es multo inferior a illo usualmente citate, 4 o 5 a 1. In le gruppos a ancestres de racia blanc, a parte le judeos, polycythemia ver occurreva con le frequentia a expectar super le base de lor representation in le population del hospital.

Ex le 197 patientes con polycythemia ver, 132 esseva mascule e 65 feminin. Le etate medie al tempore del declaration del morbo esseva 53,7 annos e non differeva inter le sexos o inter le varie gruppos de lineage. Es presentate le caso de un puero de nove annos de etate, un del plus juvene unquam reportate.

In contradiction del impression de certe autores que patientes con polycythemia ver tende a monstrar un statura svelte, nulle differentia real in altor, peso, o proportion de altor a peso esseva constatate inter le patientes con polycythemia ver e normal subjectos de controlo.

In lor representation in le gruppos de sanguine ABO, lor etate al tempore del menarche, e lor etate al tempore del menopause, le patientes con polycythemia ver non differeva ab series comparative de altere patientes al mesme hospital.

Altere disordines e morbos complicatori co-existeva con polycythemia ver in approximativemente le proportiones previemente reportate. Iste conditiones includeva hypertension (32%), arteriosclerosis (30%), ulcere peptic (14,5%), thromboses del extremitates (9,5%), dyscrasias myeloide (7,6%), e gutta (5,5%). Dece del 15 patientes con dyscrasias myeloide habeva previemente recipite radiotherapia.

Quanto al varie typos de tumor que cognoscitemente causa erythrocytosis in certe casos, hemangioblastoma cerebellar occurreva in 1% del patientes con polycythemia ver, hypernephroma in 4,4%, e myoma uterin in 33% de 39 feminas pro qui adequate historia o examine pelvic esseva disponibile. Es presentate un caso unic in que polycythemia se disveloppava in coincidentia con fibroides, dispareva post hysterectomia, e recurreva como polycythemia ver cinque annos plus tarde. Duo patientes con polycythemia e hypernephroma habeva complete remissiones hematologic post nephrectomia, de un durantia de duo e 11 annos, respectivemente. Es signalate le indication pro investigationes urologic de hematuria in patientes con polycythemia.

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EFFECTS OF CORTISONE AND ACTH IN MUMPS MENINGO-ENCEPHALITIS *

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IT has long been recognized that central nervous system involvement, most frequently aseptic meningitis or meningo-encephalitis, may occur during mumps infection.[1, 2, 3, 4] The involvement may be so mild that its presence is manifested only by abnormal findings in the spinal fluid, or it may be quite violent. The meningitis has been generally regarded as benign; however, fatalities and incapacitating sequelae have been attributed to the encephalitic component, which is quite similar to that which occasionally complicates varicella, rubeola and rubella.[5] Because no specific treatment has been available, various palliative and supportive measures have been employed. They have not been very effective in severe cases.[6] Antipyretics and sponges have had little effect on the body temperature, which may exceed 104° F. Spinal puncture and opiates have failed to relieve severe headache and painfully stiff neck. None of the means employed has been successful in combatting lethargy, delirium and more serious disturbances of central nervous system function.

Cortisone and ACTH have been reported to provide symptomatic relief when administered to patients suffering from mumps orchitis [7, 8] and mumps arthritis.[9]

Study of fatal cases of central nervous system involvement in mumps has revealed that the inflammation of the meninges is not marked, and is characterized by serofibrinous exudate and mononuclear cell infiltration.[10] Perivascular demyelinization with glial and mesodermal reaction has been described by several observers as the basic encephalitic lesion.[5, 10] Since cortisone and ACTH have become well known for their anti-inflammatory effect, and have been reported to be of benefit in certain acute demyelinating diseases,[11] it appeared reasonable to expect that they might provide symptomatic relief in mumps meningo-encephalitis and inhibit the potentially dangerous demyelinating process. On this basis these drugs were administered to five mumps patients with central nervous system involvement. This paper describes the results.

* Received for publication August 7, 1957.

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Method of Study

The five cases to be reported here were admitted to the communicable disease ward of the U. S. Army Hospital, Fort Bragg, North Carolina, during periods when the seasonal incidence of mumps was high (from early spring through early summer in 1955 and 1956). For the purpose of this study the diagnosis of mumps meningo-encephalitis was based primarily on a history of exposure to mumps, the presence of parotitis, fever, nuchal rigidity, drowsiness and/or delirium, a lymphocytic pleocytosis in the spinal fluid, normal spinal fluid sugar, normal spinal fluid chlorides, and the absence of bacteria from the spinal fluid on smear and culture. The diagnosis was confirmed in all but one case by increases in the titers of complement-fixing antibodies in convalescent as compared with acute-phase sera.* In selecting these cases a particular effort was made to obtain patients with manifestations of central nervous system involvement of no more than two days' duration (duration appreciably exceeded one day in only one case), and cases with particularly severe symptoms and signs, including disturbances of the sensorium.

Commercially available cortisone † and ACTH ‡ were used. Cortisone was administered by intramuscular route in divided doses totaling 200 to 300 mg. per 24 hours in cases where vomiting or inability to coöperate interfered with oral administration. The oral route was utilized at all times when possible, and the dosage was similar. An aqueous preparation of ACTH was used, and this was at all times administered by intramuscular injection. In all but one instance (the case of W. S.), these drugs were discontinued by progressive decrements. Reduction in the dosage generally was begun on the second or third day following institution of treatment.

Evaluation of the clinical progress in each case was based on the subjective responses of the patients, daily examination, review of the records of temperature and review of the nursing notes. Subjective responses were elicited in the usual manner. Daily examination included as complete a neurologic examination as the patient's condition would permit, and a general physical examination. For the purpose of recording these evaluations, equivocal manifestations were considered nonexistent. Evaluation of the therapeutic results was based on the comparison of these cases with cases reported in the literature, none of which had received cortisone or ACTH, and with untreated cases observed here during the same period. The latter cases will only be alluded to and not presented, because they were few in number, were much less severe, and were otherwise similar to the more numerous cases described in the literature. All cases treated with cortisone and/or ACTH are reported.

* Performed by Third Army Laboratory.

† Cortone, Merck brand of 11 dehydro-17-hydroxycorticosterone acetate, oral tablets and suspension for injection.

‡ ACTHAR C, Armour brand of corticotropin injection.

Results

Table 1 shows that the five cases studied were quite similar at the time therapy was begun with respect to symptoms, signs and laboratory findings. This was largely due to the method of selection. The patients ranged from 20 to 37 years of age. All of them experienced headache, drowsiness and stiff neck; only one did not vomit. One complained of numbness in the distribution of the left ulnar nerve, but no objective localizing signs could be demonstrated. Examination revealed nuchal rigidity and sialadenitis of one or more glands in all of the patients. All were lethargic, and three were delirious. One patient was found to have orchitis on admission. Temperatures ranged from 101 to 104° F. Deep tendon reflexes were absent in the upper extremities of patient J. M. Pleocytosis was demonstrated in the cerebrospinal fluid in every case. Mononuclear cells were found to be predominant in four cases. In one case the differential count was not performed due to laboratory error. This patient and two others had elevated cerebrospinal fluid protein. The values for sugar and chlorides in the spinal fluid were normal in all cases. Bacteriologic studies of the spinal fluids were negative. Acute and convalescent phase sera were obtained from four of the patients. Rises in complement-fixing antibody for mumps antigen were consistent with recent infection in all four.*

Three patients received cortisone and one received ACTH. One patient received one dose of ACTH, but when he showed no response cortisone was given instead. The five patients responded to treatment with reasonable uniformity, although dosage, type of drug administered and time of onset of therapy varied. Fever fell and symptoms and signs were markedly reduced within 10 to 11 hours after treatment was begun in four patients. In the case of the first patient a similar change occurred 18 hours after therapy was begun. In all cases the most marked relief was seen with respect to vomiting, anorexia, confusion, delirium and lethargy. Relief of nuchal rigidity was less marked than was relief of other manifestations.

Relapse with return of fever and central nervous system manifestations was seen 24 hours following institution of treatment in three patients. Although relapse seemed related to change from intramuscular to oral administration of cortisone in two patients (W. S. and J. M.), and to early changes in dosage schedule in another (D. C.), these relationships were not sufficiently clear to warrant any conclusions. Relapse was mild in two patients (J. M. and D. C.) who continued to receive cortisone.

Severe relapse occurred in the case of W. S., the first patient to be treated. Treatment was begun with cortisone, 50 mg. to be given every six hours. The drug was given intramuscularly at first because of the patient's severe projectile vomiting. Dramatic improvement ensued and the drug was then given by mouth. Twenty-six hours after treatment was begun the patient's

* Criteria established by Third Army Laboratory.

TABLE 1

Symptoms, Signs, Treatment with Cortisone and/or ACTH, and Response of Symptoms in Five Patients Suffering Mumps Meningo-encephalitis

Case	Age	Symptoms						Signs					Spinal Fluid		Complement Fixation†	ACTH			Cortisone			Remission of Symptoms*	CNS Relapse		Progression under Treatment		Neurologic Residuals	CNS Recovery Complete
		Headache	Drowsiness	Stiff Neck	Vomiting	Focal Symp.	Local Signs	Nuchal Rig.	Delirium	Sialadenitis	Orchitis	Fever	Pleocytosis	Protein Elevation		Dose	Begun*	Last Dose*	Dose	Begun*	Last Dose*		Time*	Severe	Sialadenitis	Orchitis		
W. S.	28	+	+	+	+	+	0	+	+	+	0	101	+	+	—	—	—	—	50 mg. q6h IM	48	68	58	74	+	—	—	0	144
J. M.	20	+	+	+	+	0	+	+	+	+	0	103	+	+	+	20 mg. IM	17	17	75 mg. q6h IM	37	408	48	61	0	+	0	0	96
W. M.	37	+	+	+	0	0	0	+	0	+	0	104	+	0	+	—	—	—	50 mg. q6h P.O.	26	216	36	—	—	+	+	0	36
R. S.	20	+	+	+	+	0	0	+	+	+	0	101	+	+	+	15 mg. q6h	24	146	—	—	—	34	—	—	—	—	0	34
D. C.	20	+	+	+	+	0	0	+	0	+	+	104	+	0	+	—	—	—	75 mg. q6h P.O.	20	264	38	44 ‡	0	—	—	0	82

* Hours after onset of two or more CNS symptoms.
† Rise in titer fourfold or titer greater than 1 : 128.
‡ Six a.m. dose of cortisone omitted 2nd day of treatment.

temperature again began to rise. Since the reason for this was not clear, no more cortisone was given. The patient was soon as ill as at the time of admission. Gradual improvement began two days later, and recovery was complete six days after admission. Recovery was complete in 36 hours in two patients. Two patients who may have been more severely ill recovered 96 hours after hormone therapy was begun. The dosage of the drugs was progressively decreased over a period of several days in four cases. Treatment lasted five days in one case, eight days in one case, 10 days in one case, and 16 days in one case. In no instance was a recrudescence of central nervous system manifestations observed during gradual reduction in dosage. The time of recovery from sialadenitis did not appear to be prolonged, and the over-all duration of the illness was similar to that of uncomplicated mumps. Two patients experienced additional salivary gland involvement during the treatment period. Orchitis developed in one of these patients during treatment with cortisone.

Discussion

In the selection of patients with mumps meningo-encephalitis for treatment with cortisone and ACTH, only those with clinically severe central nervous system manifestations were chosen. Clinical manifestations appeared to provide the most acceptable criteria of severity, since it has been shown that cerebrospinal fluid changes do not correlate well with severity of involvement.[1, 5] Symptoms of headache, stiff neck and vomiting, and physical signs of nuchal rigidity and fever, occur in most clinically manifest cases of the disease and present a continuous distribution of degrees of severity. Drowsiness, however, is less frequent, having been reported in only 12 of 106 cases of manifest mumps meningo-encephalitis by Bang and Bang,[2] in four of 20 cases by Silwer,[1] and in 12 of 25 cases by Riege and Smith.[4] Eberlein and Lynxwiler [3] reported drowsiness in 53% of a series of cases in children gathered from the literature. Miller, Stanton and Gibbons [5] presented 27 highly selected cases from the literature which they considered to have suffered a primarily encephalitic type of illness. Among these cases they found drowsiness an invariable feature, and delirium present in 44%. The cases presented in table 1 seemed, therefore, of unusual severity.

The administration of cortisone in four cases and ACTH in one case seemed to have a palliative effect on the severity and duration of symptoms and signs. Evaluation of such effects was difficult due to the small number of subjects. The occurrence of remission 10 to 11 hours after institution of hormone therapy in four patients and after 18 hours in one patient, regardless of the duration of illness prior to therapy, appears to be convincing evidence of a definite palliative effect. Selling and Meilman [11] have apparently used a similar time interval as a criterion in evaluation of the effects of ACTH in acute disseminated encephalomyelitis. No similar abrupt

change in the clinical picture was reported in the numerous untreated cases in the literature. The dramatic relapse and subsequent course of W. S. (table 1) furnished strong presumptive evidence of the efficacy of cortisone as a palliative agent.

Evaluation of the effects of these drugs on the over-all duration of fever and central nervous system manifestations is more difficult. The treated cases may have experienced complete and permanent remission sooner than other, milder cases admitted during the same period. Differences in over-all duration of symptoms, regardless of degree, were not great, being only a few hours or days. Comparison with untreated cases in the literature was difficult because of individual variation. Silwer [1] reported duration of fever (presumably from time of admission) to range from one to six days (average, four days). Eberlein and Lynxwiler [3] reviewed many reported cases of the untreated disease and showed various figures, most of these within a range of from three to seven days. Kilham, Levens and Enders [12] reported a mean duration of symptoms of eight and one-half days in six cases of mumps meningo-encephalitis without parotitis or orchitis. Even by conservative standards, it would appear that the persistence of central nervous system symptoms was not prolonged in the cases reported in table 1.

The over-all duration of mumps was not prolonged in any of the patients treated with cortisone or ACTH. This statement is based on more than three years' experience with the disease at this hospital. The occurrence of additional salivary gland involvement and the development of orchitis during treatment probably were not related to the method of treatment, as it is well known that this occurs in untreated patients.[1, 3] The occurrence of orchitis during cortisone therapy is noteworthy, since it has been reported to be amenable to palliation with ACTH and cortisone.[7, 8] No mention of early remission and relapse in untreated mumps meningo-encephalitis was found in the literature. Bowers and Weatherhead [6] remarked that secondary temperature rise indicates other mumps involvement. This could not be established as a factor in the febrile relapse seen during hormone therapy, although the possibility was not excluded.

The present study has provided no basis for explanation of any effects which ACTH or cortisone may have had on the patients. It is still an open question as to whether mumps meningo-encephalitis is due directly to proliferation of virus in the central nervous system [10, 12, 13] or to an allergic type of phenomenon such as is found in postvaccinal encephalomyelitis,[5] or perhaps both. If the first possibility were true, one would suspect the anti-inflammatory effects of the drugs were inhibiting tissue response to the multiplying parasite. If the second explanation were correct, inhibition of tissue response to antigen-antibody reactions would be suspect. In the latter event the effects would be highly desirable, and treatment with cortisone and ACTH might reasonably be extended to other para-infectious encephalomyelitides.[5] It has been shown that perivascular demyelinization, absence

of leukocyte reaction in the brain and sparing of nerve cells are common to these syndromes and to postvaccinal encephalitis.[5, 10] These drugs have already been reported to be of benefit in postvaccinal encephalitis [11] and rubella encephalitis.[14]

Although isolation of mumps virus from the cerebrospinal fluid of patients with mumps meningo-encephalitis has been reported,[12, 13] the virus has not been isolated from brain tissue. Furthermore, the pathologic alterations due to this disease are reported to differ considerably from those of the encephalomyelitides [5, 10] known to be due to viruses such as St. Louis or Japanese B encephalitis. If mumps meningo-encephalitis is assumed to be due to multiplication of the virus in the central nervous system, then the possibility that host resistance to the virus would be impaired must be considered. The potential hazards implicit in the use of cortisone and ACTH in patients with viral diseases have been extensively reviewed.[15, 16, 17] The information which has provided the basis for these reviews was derived principally from animal experiments [18, 19, 20] in which conditions and drug dosages were considerably different from those customarily used therapeutically in humans. The use of these drugs in various viral diseases in humans has apparently resulted in no difficulty, and benefit has been reported in some cases.[17] Reports of adverse effects seem for the most part to have been confined to patients who became ill with varicella during therapy with cortisone or ACTH.[21, 22] None of the patients with mumps meningo-encephalitis in the present report showed any evidence of adverse effects during or following treatment with these drugs.

Tuberculous meningitis produces a clinical picture and laboratory findings similar to aseptic meningitis. Since administration of cortisone or ACTH without appropriate antimicrobial agents would be particularly undesirable in tuberculous meningitis, care must be taken to exclude this disease.

The diagnosis of mumps meningo-encephalitis can be made with reasonable certainty on the basis of: a history of recent exposure to mumps, presence of mumps in the community and a negative past history for mumps, physical signs of salivary gland inflammation, and laboratory findings of a predominantly lymphocytic pleocytosis in the spinal fluid with normal values for spinal fluid sugar and chloride and negative bacteriologic examination of the spinal fluid by smear and culture.

Summary

The efficacy and safety of cortisone in the symptomatic treatment of four patients with severe or moderately severe mumps meningo-encephalitis have been investigated. A fifth patient was treated with ACTH (corticotropin). Diagnoses were confirmed by lumbar puncture in all cases, and complement fixation titers were determined in four.

Cortisone was administered in doses of 200 to 300 mg./day, and ACTH

in doses of 60 mg./day. In all cases but one the drugs were discontinued by progressive decrements.

Cortisone and ACTH appeared to produce rapid remission of headache, nausea, anorexia, vomiting, photophobia, lethargy, delirium and nuchal rigidity. Fever, although it fell rapidly, tended to return to previous levels for short periods of time, accompanied by minor recurrence of other symptoms. Orchitis developed in one patient during cortisone therapy. This patient, and one other, suffered additional salivary gland involvement during therapy. Abrupt termination of therapy in one case after three doses of cortisone resulted in a dramatic recurrence of previous symptoms.

The duration of mumps in these patients was not shown to differ from that in patients not receiving cortisone or ACTH. No evidence of residual disease of the nervous system could be detected in any of the patients.

SUMMARIO IN INTERLINGUA

Esseva investigate le efficacia e le salvitate del uso de cortisona (acetato de 11-dishydro-17-hydroxycorticosterona) in le tractamento symptomatic de quatro patientes con grados sever o moderate de meningo-encephalitis a parotiditis. Un quinte patiente esseva tractate con ACTH (hormon adrenocorticotropic). Le diagnose de meningo-encephalitis a parotiditis esseva basate super un historia de exposition a parotiditis, le presentia de inflammation del glandulas parotide, febre, rigiditate nuchal, somnolentia e/o delirio, un pleocytose lymphocytic in le fluido spinal, normal nivellos de sucro in le fluido spinal, normal nivellos de chloruros in le fluido spinal, e le absentia de bacterios in frottis e culturas de fluido spinal. Le titros de anticorpore a fixation de complemento pro antigeno de parotiditis accresceva significativemente in le seros de quatro patientes. Le duration del symptomas del systema nervose central ante le tempore del hospitalisation excedeva un die in solmente un caso; illo excedeva duo dies in nulle del casos.

Cortisona esseva administrate in doses de 200 a 300 mg per die, ACTH in doses de 60 mg per die. Cortisona esseva administrate per via oral, excepte quando le vomito esseva si sever que le via intramuscular debeva esser usate. ACTH esseva administrate intramuscularmente. Ambe le drogas esseva administrate a intervallos de sex horas in doses equalmente dividite. In omne le casos, con un exception, le cessation del drogas esseva effectuate per reductiones progressive. Recrudescentia del manifestationes in le systema nervose central durante le reduction gradual del dosage non esseva observate in ulle del casos.

Le administration de cortisona o de ACTH esseva sequite intra circa 12 horas per remission del mal de capite, del nausea, del anorexia, del vomito, del photophobia, del lethargia, del delirio, del febre, e del rigiditate nuchal. Isto valeva in omne le casos. Febre e—minus pronunciatemente—alteres del symptomas tendeva a recurrer circa 24 horas post le initiation del therapia hormonal. Iste recidivas durava solmente alicun horas. Orchitis se disveloppava in un patiente durante le therapia per cortisona. Iste patiente—e ancora un altere—suffreva additionalmente affectiones de glandula salivari durante le curso del therapia. In uno caso, le abrupte termination del therapia post tres doses de cortisona resultava in un recurrentia dramatic del previe symptomas. Iste patiente se restabliva completemente sed solmente post sex dies de hospitalisation.

Non se notava que le duration del parotiditis in iste patientes differeva ab illo in patientes qui non recipeva cortisona o ACTH. Nulle signo de morbo residue del systema nervose poteva esser detegite in ulle del patientes.

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PLEURITIS IN SYSTEMIC LUPUS ERYTHEMATOSUS: ITS IMPORTANCE AS AN EARLY MANIFESTATION IN DIAGNOSIS *

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INTRODUCTION

ALTHOUGH pleuritis and pleural effusion have long been considered as cardinal signs in the clinical picture of systemic lupus erythematosus (S. L. E.‡), these have usually been regarded as late manifestations of the disease. The feeling also prevails that unexplained pleuritis is to be regarded as tuberculous or neoplastic unless proved otherwise. However, now that the early diagnosis of S. L. E. has been facilitated by the "L. E. cell preparation," it seems well to reëvaluate pleuritis as an early sign in S. L. E. Moreover, the striking improvement in prognosis with steroid treatment makes an early diagnosis much more significant.

Our interest in the problem was stimulated by two very similar cases of relatively isolated pleuritis occurring in young females who had negative tuberculin tests and who showed repeatedly positive L. E. preparations in the absence of any of the known causes of false-positives. In view of these findings, a diagnosis of S. L. E. was highly probable.

CASE REPORTS

Case 1. A 22 year old white female was admitted to Montefiore Hospital in February, 1954, because of pleural effusion. A month before she had been hospitalized elsewhere for sudden left pleuritic pain, fever, cough and hemoptysis, all of which had disappeared within a week save for some residual chest pain. X-rays had shown only "pneumonitis at left base," clearing wholly; but one week later a check-up film had revealed a left pleural effusion. There had been a weight loss of 17 pounds in one year. There was no history of drug sensitivity, liver disease, diabetes, or other cause of "false-positive" L. E. preparations.

Physical examination was unremarkable except for decreased breath sounds at the left base; no râles or rhonchi were heard. X-ray showed a small left pleural effusion, with no parenchymal lesion; laboratory studies were negative save for albuminuria varying between 2 plus and 0. The patient was promptly transferred to

* Received for publication June 24, 1957.

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† American Trudeau Society Fellowship, 1955–1956.

‡ This abbreviation for systemic lupus erythematosus is used throughout this paper.

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a sanatorium where, after repeatedly negative tuberculin tests, a L. E. preparation was found to be positive. The effusion cleared spontaneously and, after several more L. E. preparations were strongly positive, the patient was discharged asymptomatic. No further follow-up is obtainable as yet.

Case 2. A 41 year old Negro female was admitted at another institution in August, 1955, complaining of bilateral chest pain. Past history was essentially negative. Physical examination revealed signs of a right pleural effusion, confirmed by x-ray. Diagnostic studies were essentially negative, and several thoracenteses were done, with symptomatic improvement. After one month of hospitalization the fluid resorbed and the patient was asymptomatic. During the summer of 1955 she had thrombophlebitis in the left lower extremity. This recurred in December, 1955.

When the patient was seen at Montefiore Hospital in January, 1956, physical examination was unremarkable except for some nodularity in both breasts. Chest x-ray revealed residuals of pleural reaction on the right. Blood urea nitrogen was normal; urinalysis revealed 1 plus albuminuria; blood total protein was 8.7 gm.%, with a globulin of 4.2 gm.; L. E. preparations were highly positive on several occasions. Mantoux was negative to a dilution of 1:100.

The clinical story of pleural effusion, thrombophlebitis with elevated blood globulins, positive L. E. preparations and albuminuria would suggest that the patient had S. L. E. which was relatively quiescent at the time of the last examination.

Both of these cases would have been diagnosed as S. L. E. in many clinics, and follow-up will most likely prove the point. Our experience with these patients led to a study of the frequency of early pleuritis in a group of proved cases of S. L. E. in order to throw light on the early diagnosis of the disease. As will be shown in this paper, out of a consecutive series of 57 well proved S. L. E. cases whose x-rays were studied, three had typical pleuritic pain as the *first* hint of the disease, with effusion appearing soon after in two, and later in the third. Sixteen others had pleuritis early in the course of S. L. E., among whom 11 were frank effusions. Such data would seem to place S. L. E. high on the list of possible causes of any "unexplained" effusion.

Review of Literature

A. *Studies of "idiopathic" pleuritis:* Most authors indicate that the old practice of attributing "idiopathic" pleuritis to tuberculosis or neoplasm has been gradually giving way to recognition of other frequent causes. Barnwell, in Cecil's textbook,[3a] lists among the causes of pleural effusion not only the malignancies, Hodgkin's and the noninflammatory group, including cardiac failure, cirrhosis, renal disease and anemia, but also subphrenic abscess, actinomycosis, rheumatic fever, virus pneumonia and Meigs's syndrome. It is of interest that the collagen diseases are not included here, although most other recent texts at least describe the possibility of such origin.[4, 19, 36]

Of the detailed recent studies, Leuallen and Carr,[26] reviewing 436 consecutive cases of primary pleural effusion, give perhaps the most representative sampling of this entity. They found only 5.5% of tuberculous origin,

52.5% of neoplastic and 10.0% of cardiac, while 1.0% (or four) of the other cases were traced to lupus.

For contrast, Roper and Waring,[35] in a study of 141 soldiers showing "primary . . . pleurisy with effusion and without evidence of preëxisting tuberculous disease," found 51 to have tuberculosis at the time of effusion, while 59 more developed that disease during follow-up. The remaining 31 men were also presumed to have had tuberculosis. All of the men were followed for five or more years.

Similarly, Skaggs and Smiley [39] followed 50 cases of "idiopathic" effusion, 22 of whom were females; eight proved to be tuberculous, and the rest were presumed to be so.

Earlier, Falk [11] had reviewed several series from the literature, finding ultimate proof of tuberculosis in 20% to 40%, and giving no other diagnosis for the remainder.

Two smaller series are worth noting, since they involved pleural biopsy in cases of long-continued pleuritis, usually with effusion, which had defied diagnosis. Stead et al.[42] explored surgically 24 patients of this type (23 were male), and found 15 to be tuberculous, four with underlying "organizing pneumonia," and the rest due to various causes, none of which was collagen disease. Small and Landman [41] biopsied five such cases, finding tuberculosis in all.

We conclude, as summarized by Shane,[37] that most observers still regard pleuritis as tuberculous or neoplastic until proved otherwise, although the *possibility* of collagen disease is receiving a somewhat tardy recognition.

B. *Pleuritis in S. L. E.:* Pleuritis has long been known to be one of the common signs of this disease, but only through the recent recognition of early or atypical cases of S. L. E. has it begun to be considered as a possible *early* sign. For example, in 1949 Montgomery and McCreight,[30] reviewing 20 years' experience at the Mayo Clinic, made no specific reference to pleuritis save as "polyserositis"; it was not mentioned in their suggestions of diagnostic signs, nor was pneumonitis.

Among the more recent reviews, the definitive one of Harvey et al.[15] well summarizes the pleural changes of the disease; they are peculiarly episodic and isolated, often clearing before any diagnosis of S. L. E. is made. In at least 13% of their series pleuritis recurred one or more times. It was found in 56% of all the cases, although effusion was observed in only 16%, the fluid tending even then to be small in amount. Those who had pneumonitis usually had associated pleuritis, but the converse was not true: pleuritis often occurred independently.

Gould and Daves [13] reviewed the x-rays from the Harvey series. Employing unusually careful methods to detect minimal pleuritis, they found signs of such lesion in 74% of the cases. Tumulty [44] had a very similar experience. In a brief summary he stressed that, aside from the arthritis

TABLE 1

% Incidence of Certain Manifestations of S. L. E.
(Figures in parentheses = per cent manifesting at *onset* of S. L. E.)

Author*	Number of Cases	% Fever	% Arthritis, or Arthralgias	% Rash (All Types)	% Cardiac Disease (All Types)	% Pericarditis	% Renal Disease (All Types)	% Pleuritis (Incl. Effusion)	% Pleural Effusion	% Pneumonitis (All Types)	% Anemia	% Leukopenia	% Thrombocytopenia or "Purpura"	% False-Positive S. T. S.	% Raynaud's Phenomena
Harvey et al.[15]	105	86 (23)	90 (32)	85 (20)	52 —	45 (1)	65 (5)	56 (5)	16 —	45 (1)	78 —	— —	26 (1)	15 —	10 (3)
Jessar et al.[22]	44	95 (25)	77 (48)	68 (14)	70 —	23 —	70 —	— —	39 —	20 —	95 —	70 —	— —	28 —	16 (11)
Dubois[8]	62	97	90	52	—	44	57	60	55	—	78	68	10	33	26
Moersch et al.[29]	54	—	—	—	—	—	—	—	19	23	—	—	—	—	—
Garland and Sisson[12]	32	—	—	—	—	16	—	—	41	31	—	—	—	—	—
Meacham and Weisberger[27]	25	(12)	(32)	(16)	—	(4)	(8)	(0)	(0)	—	—	—	20 (12)	28 (8)	20 (8)
Leikola and Vartia[25]	20	90	80	40	—	20	35	40	—	—	—	—	—	—	—
Shearn and Pirofsky[43]	34	100	85	91	—	18	62	50	24	—	97	74	31	19	6
Thorell[45]	15	—	—	—	—	—	—	46	13	—	—	—	—	—	—
Israel[20]	23	—	—	—	—	—	—	—	9	77	—	—	—	—	—
Total + Averages:	414	92%	86%	71%	58%	33%	62%	54%	28%	38%	84%	71%	22%	23%	15%

* Gould and Daves[13] and Tumulty[44] are omitted, since their cases are covered by Harvey et al.
Klemperer et al.[23] covered only autopsy material, while Montgomery and McCreight's data[30] could not be classified in the above table.

or the rash, no other symptom of S. L. E. tends to clear as frequently and completely as does the pleuritis.

Table 1 summarizes the available recent series as to incidence of the major signs of S. L. E., and the time of onset, when given. Only three authors give data on timing of pleuritis, and these only on its incidence as a "presenting symptom." Most of the others imply that pleuritis usually occurs late, even terminally, in the disease.[29]

As to the occurrence of pleuritis in relation to age or sex, or to the other symptoms of S. L. E., we found no data save those outlined in table 1. Detailed studies have been published on the early appearance in lupus of such manifestations as false-positive S. T. S.,[32] thrombocytopenic purpura and hemolytic disorders,[27] but there has been none on the early pulmonary or pleural signs of the disease, other than the general discussions of presenting symptoms.

C. *Pathogenesis:* Little has been written on the pathogenesis of pleuritis in lupus.[31] This may be attributed to the fact that at autopsy one sees the end result of many successive episodes: usually there is terminal effusion, and often fibrosis obliterates any other lesions originally present. Purnell et al.[33] discuss the question thoroughly, describing autopsies in varying stages of organization of the fibrinous exudate, often with old fibrosis underlying. In 1941 Klemperer et al.[23] described the basic fibrinoid degeneration of collagen in connective tissue and vessels throughout the body, but this was only

occasionally detected in the pleura. It is more often overlaid by a secondary response to adjacent pneumonitis, whether the latter was itself caused by lupus or by infection. The hematoxylin bodies, considered diagnostic by Klemperer and others,[14, 24] have to date been found in only a few of the pleura examined.[14]

Much more was found on the pathology of the pneumonitis of lupus. Like the pleuritis, it is notably migratory;[27] it tends to affect the lower lung fields, to show platelike atelectatic areas as well as patchy infiltrates, with elevation and fixation of diaphragms;[13, 15] in addition, Thorell[43] notes a tendency toward subpleural localiization.

Beyond the preceding, there is little agreement about the pathologic process in the lungs. Many episodes are found to be infectious,[20] but only

TABLE 2

Chief Methods of Ruling Out Causes of Pleuritis* Other Than S. L. E.

	Congestive Failure	Tuberculosis	Other Bact. Infec.	Viral Infec.	Neoplasm
Normal venous pressure plus clinical data	5				
Clinical data (without venous pressure)	14				
Effusion cleared on steroids without cardiac drugs	7				6
Effusion cleared without steroids					9
Absence of effusion	7				6
Negative Mantoux (in absence of steroids)		5			
Clinical grounds (incl. at least two of these: (1) neg. bacteriology; (2) normal or low W.B.C.; (3) no response to antibiotics)			3		
Absence of pneumonitis, x-ray or clinically			21	24	
Prolonged course: on steroids		11†			
no steroids		3‡			
Cytology on pleural fluid					2
Autopsy		9			9
Not well ruled out§	0	5	9	9	1

* Cases omitted are those shown in table 3 as either late pleuritides (coming only after diagnosis of S. L. E.), or having obvious coexisting disease.

† Average duration of this follow-up was 23 months.

‡ Follow-ups were, respectively, 24 months, 14 months and 18 years.

§ Some of these cases had more than one *possible* other cause for pleuritis. Only 11 had any such cause or causes "not well ruled out." The remaining 22 are rigidly established lupus pleuritis cases.

TABLE 3

Types and Relative Timing of Pleuritis in 57 Cases of S. L. E.
(X-rays available)

		Pleural changes (to x-ray)			Pleuritic pain	Total with pleuritis	No pleuritis attributable to S. L. E.
		Effusion	No effusion				
			With pleuritic pain	No such pain			
"Early"	Pleuritis as first manifestation of S. L. E.	0	0	0	3*	3	16
	Preceded by less than 2 major manifestations of S. L. E.	11	1	0	4†	16	
"Late"	Preceding working diagnosis of S. L. E.	4	2	0	0	6	
	After diagnosis, yet not terminal	6	0	2‡	0	8	
	With other complicating disease§	6	2	0	0	8	
	Totals	27	5	2	7	41	

* All these developed pleural effusion, two simultaneously with the onset of other initial symptoms of lupus, the other later in the course of S. L. E.

† Three of these showed x-ray signs of pleuritis later, after repeated pleuritic symptoms.

‡ These are the two cases described on page 77, under C.

§ Of these, four had known or suspected tuberculosis, and one each had the following: bacteremia, congestive failure, pulmonary infarct, and postoperative atelectasis with pneumonitis.

Baggenstoss [2] seems to have found a specific "lupus" lesion, i.e., a "mucinous edema of alveolar walls and . . . (connective) tissues." Nevertheless, even he found no trace of "fibrinoid degeneration" in the lungs of his 54 cases, and concluded that "there is no pathognomonic pulmonary lesion" in S. L. E. The "hematoxylin bodies" have so far been found in only a very small proportion of lungs examined.[14]

As to the relation of pleuritis to effusion, autopsy almost always reveals terminal effusion if the pleura was at all involved. Table 1, however, shows that 54% of the cases reviewed had pleuritic changes, but only 28% had effusion. Also, in the careful radiologic study by Gould and Daves,[13] only 21 of the 74 with pleuritis developed *detectable* fluid. A "dry pleurisy" therefore seems a very common occurrence in S. L. E.

There seems to be general agreement that pleuritis in lupus tends to be bilateral,[13] often alternating sides; [15] that the fluid, if any, is an exudate, with a relatively low polymorphonuclear count, and may demonstrate the L. E. cell phenomenon.[36] There is also agreement that in S. L. E. infections are common, with pneumonitis unusually frequent. Yet it appears that true

"lupus pneumonitis" often occurs. The following criteria for it are given by Harvey:[15] prolonged toxic course despite antibiotics, sputa negative for pathogens, minimal output of sputum, relatively few physical findings or local symptoms, and x-ray changes as outlined above.

D. *Criteria for Diagnosis:* Efforts to find a firm basis for the diagnosis of S. L. E. were poorly rewarded. There are many reasons for this. Even complete autopsy may be inconclusive, since the disease seems to affect the various organs capriciously. The "fibrinoid degeneration" is indistinguishable from that of other collagen diseases.[14] Montgomery and McCreight,[30] moreover, were unable to find this lesion in 75% of their 286 cases of S. L. E. The "hematoxylin bodies," even under close scrutiny, may not be detected in certain proved cases of the disease. Finally, wide use of the adrenal steroids apparently permits complete "healing," with minimal fibrosis of some lesions, by the time autopsy is performed.

Establishing the diagnosis in life is just as difficult. No rigid standards exist. Some authors seem confident that positive "L. E. cell" preparations are sufficient if drug reactions are ruled out.[8, 16, 27, 38] However, this confidence is likely to be shaken by recent descriptions of false-positive L. E. cell results, proved by autopsy, in such chronic diseases as tuberculosis,[21] cirrhosis, hepatitis,[17] diabetes and rheumatoid arthritis on large maintenance steroid dosage.[40] Furthermore, there is ample evidence that S. L. E. patients can repeatedly show negative L. E. preparations, even after having several positive ones.[22]

Skin and muscle biopsy might seem an aid in diagnosis, but this, too, can be confusing. Many other diseases, such for example as dermatomyositis,[44] show similar nonspecific changes. Also, the number of false-negative biopsies is discouragingly high.

Of the authors consulted, only Harvey et al.[15] and Jessar et al.[22] attempted to list criteria for diagnosis, aside from autopsy, biopsy, L. E. preparation or "clinical data"; but even their formulae were admittedly subjective.

We have avoided discussion of the diagnosis of "discoid lupus," whether "localized" or "generalized,"[7] since it is generally agreed that this frequently merges into S. L. E., our primary concern.

Materials and Methods

A. *Selection of Cases:* At the Montefiore and New York Hospitals we reviewed the charts and studied the available x-rays of all patients diagnosed as S. L. E. from 1945 to the present. Diagnosis was established beyond reasonable doubt through the following criteria:

1. All cases with an autopsy diagnosis of S. L. E. were included.
2. No other case was included unless the final diagnosis of the medical staff was S. L. E. If there was any doubt as to the diagnosis the case was eliminated. Follow-ups were carefully checked either with the patient's personal physician or at the hospital clinic. Finally, all those were eliminated who presented less than four points in the following scheme:

Major Manifestations (one point each)	Minor Manifestations (half-point each)
Arthritis, rheumatoid type	Arthralgias or atypical arthritis
Typical	Atypical rash
Unexplained fever, prolonged	Raynaud's phenomena
Unexplained pleuritis } not over	Marked constitutional symptoms other than fever
Unexplained pericarditis } 2 points	Unexplained anemia *or* leukopenia *or* thrombocytopenia
Unexplained peritonitis } in all	Unexplained hepatosplenomegaly *or* generalized adenopathy
Unexplained cardiac disease	Compatible skin or muscle biopsy
Unexplained renal disease	Typical retinal lesions*
Unexplained C. N. S. lesions	Typical "lupus pneumonitis"†
Bone marrow depression (at least two of the following: anemia, leukopenia, thrombocytopenia)	Elevated serum globulins
Positive L. E. cell preparation	Biologic false-positive S. T. S.

* As described by Tumulty[44].
† As described above (page 76).

B. *Establishment of "Pleuritis":* When fluid was demonstrated clinically, this was considered proof of pleuritis, whether or not symptoms occurred. When no effusion was detected we looked for a history of pleuritic pain. If established, the affected side was studied for x-ray signs of pleural thickening, at a costophrenic angle, along the leaves of the diaphragm, or up the lateral wall. Criteria used are outlined by Gould and Daves.[13] In the two cases where x-ray changes were recorded without a history of recent pleuritic pain, we included only lesions gross enough to be mentioned on any routine reading. If no findings appeared save the history of pleuritic pain, results were recorded as such. Pleuritis occurring in only the last week of life was excluded from our tabulation.

C. *Establishment of S. L. E. as a Cause of Pleuritis:* No episode was considered to be due to lupus unless there was frank effusion or *recent* history of pleuritic pain (save for two cases, one with x-ray changes under observation, the other with frequent pneumonitis attributable to lupus). When such history was present, the criteria shown in table 2 were applied to rule out the chief possible other causes of pleuritis. (Where more than one method is applicable, only the most satisfactory one is mentioned.)

Results

A total of 77 cases were found to have proved S. L. E.: 23 by autopsy, 54 by the criteria given. Of the 54, 15 actually had six "points" or more. Of the 77, only three were males; 10 were less than 20 years old; eight were over 50 at the time of diagnosis.

Table 4

Major Symptoms Preceding Pleuritis

(All uncomplicated cases of S. L. E. with pleuritis occurring before diagnosis of S. L. E.)

Arthritis or arthralgias	12
Arthritis and rash	4
Arthritis and Raynaud's	2
Arthritis and purpura	2
Arthritis and marked fever	2
Fever only	1
Rash only	1
Rash and Raynaud's	1
Rash and renal disease	1
None	6
Total	32

TABLE 5

Mean Survival Time Following the First Pleuritic Episode in S. L. E.
(All cases without known coexisting pleural disease)

	No. of Cases	Mean Survival	No. Still Alive*
Pleuritis occurring before diagnosis of S. L. E.	30	41.4 months	16
Pleuritis occurring after diagnosis of S. L. E.	12	36 months	7

* One case is known to be alive 20 years and another died 17 years after onset of pleuritis and S. L. E.

There were 57 cases whose x-rays were available for study. Incidence and time of onset of pleuritis in these patients are given in table 3.

There were 20 additional cases whose x-rays had been destroyed. Their official readings were as follows: two showed effusion (one "early," one "late," as defined in table 3); two had pleuritic pain early, with x-ray changes as soon as films were taken; one had x-ray changes as soon as films were taken; one had x-ray changes "late"; three had "late" pleuritic pain; one had effusion with pulmonary infarct; the remaining 10 had none.

It is significant that among the 22 cases whose diagnoses were proved at autopsy, the incidence and time of pleuritis were closely similar to those of the group as a whole.

Data on symptoms appearing before onset of pleuritis are shown in table 4. The preponderance of arthritic symptoms is striking.

Of the manifestations coinciding with pleuritis, there was no significant correlation save with (a) pericarditis, and (b) pneumonitis. Pericardial involvement occurred in only eight of the 32 cases showing pleuritis (as

TABLE 6

Outcome of Pleuritis
(All cases without known coexistent pleural disease, where x-ray changes were detected)

	With Effusion		Without Effusion		Total
	Treated (Steroids)	Untreated	Treated (Steroids)	Untreated	
No. clearing one or more episodes; no x-ray residue	8	4	1	1	14
No. clearing; minimal pleural changes remaining	2	6	0	0	8
No. with pleuritis not subsiding	1	6	0	5	12
No. with inadequate x-ray follow-up (less than 2 weeks)	1	0	1	3	5
Total	12	16	2	9	39

TABLE 7

Location of Pleuritis
(All cases without known coexistent pleural disease)

	Effusion	Pleuritis Without Effusion
Bilateral, simultaneous	11	6
Alternating sides	4	2
Left-sided only	4	9
Right-sided only	4	2
Total	23	19

described in table 4). Pneumonitis also was rather infrequent. Of the 32 cases, 21 had at least one episode of pleuritis without pneumonitis detectable through history, physical examination or x-ray.

Many other manifestations of S. L. E. were present during pleuritic episodes, but no more frequently than at other stages of the disease.

In view of the tendency to remission after pleuritis in S. L. E., it was interesting to note the duration of life after the first known pleuritic episode.

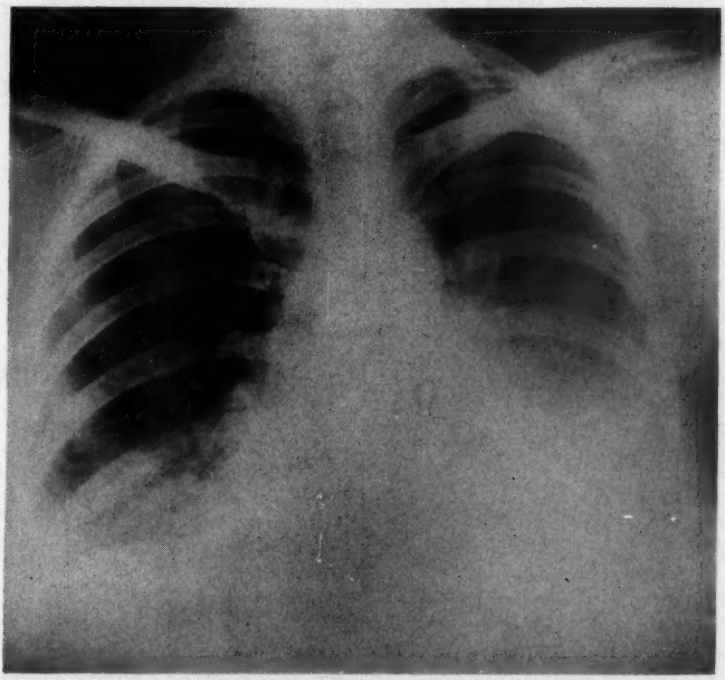

FIG. 1A. A 37 year old female had had arthritis for 16 years. S. L. E. had been suspected for 10 years, and had been definitely established clinically in 1954. Two documented episodes of pleuritis had occurred (February and August, 1954). The present film (11/11/54) shows clouding of the entire left hemithorax and obliteration of the costophrenic angle, as well as a large heart, vascular congestion and a blunted right costophrenic angle.

This is summarized in table 5. Since 23 of these patients were alive when last reviewed, the final data on survival will be notably beyond the values shown.

Further evidence of the favorable prognosis following pleuritis in S. L. E. is given in table 6. This shows the number of cases with clearing of one or more episodes, whether with or without therapy, where x-ray evidence was obtainable (figures 1A, 1B, 1C; and figures 2A and 2B).

Data on the location of pleuritis are shown in table 7. Almost half of the patients had only one side involved; only 17 of the 42 had bilateral simultaneous involvement. The predominance of left-sided lesions is of possible significance.

To confirm the validity of the criteria used (see page 77) we reviewed all autopsied cases diagnosed as S. L. E. at either of the two hospitals at some time during life. Our clinical impressions were then compared with the pathologic findings. There were 24 cases fulfilling our four "points," 21 * of which were conclusively S. L. E. at autopsy. Among the remaining

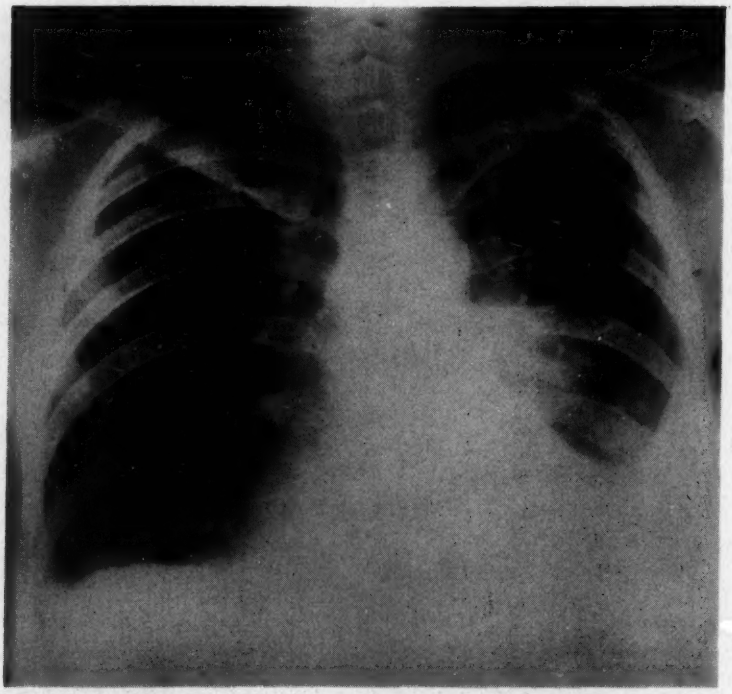

FIG. 1B. 11/13/54. Some decrease is seen in the amount of fluid, but now a clear line of effusion extends up the lateral chest wall. Pulmonary congestion is decreasing; other findings are unchanged.

* 18, New York Hospital; three, Montefiore Hospital.

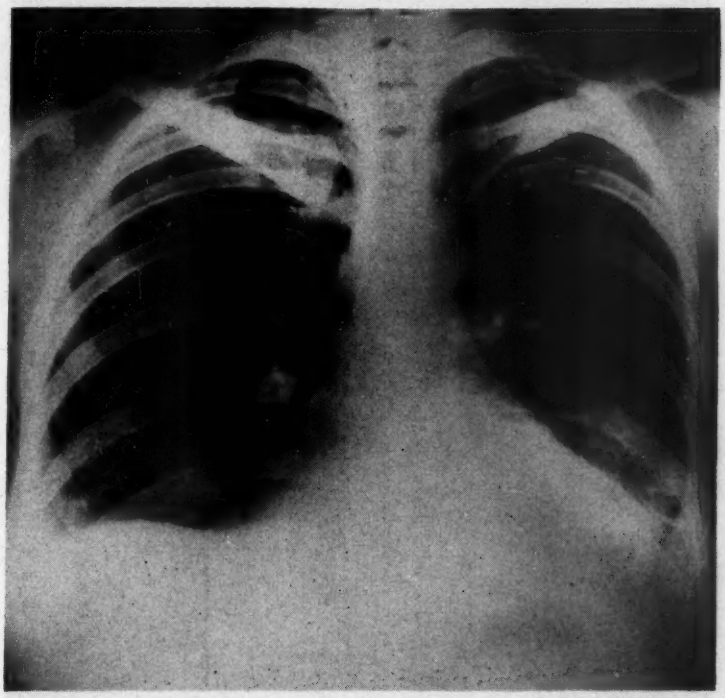

FIG. 1C. 11/23/54. Cortisone has been administered for the first time (11/20/54). The pleural fluid has been almost completely resorbed, with residual changes, either pleural or parenchymal, at the left costophrenic angle.

three, one proved to be periarteritis nodosa; two had atypical findings. Of these two,* the one presented below had had extensive steroid therapy and showed lesions consistent with the diagnosis of arrested or "healed" lupus.

Case 2. A 28 year old Negro female had had arthritis of rheumatoid type with intermittent chills and fever since early 1951. In April of the same year, butterfly rash and alopecia appeared. Pleuritis with friction rub and effusion were noted two months later. Thereafter she was seldom free of dyspnea and chest pain. In 1954 and early 1955 she had bouts of pneumonitis with episodes of cardiac failure. A definite diagnosis of S. L. E. was made in November, 1954. Cortisone was soon begun, and was continued throughout her course.

On October 5, 1955, she entered Montefiore Hospital in respiratory distress, with tachycardia and systolic murmurs, and presenting 2 plus albuminuria. The blood urea nitrogen was 25; A/G ratio, 3.1/3.6. There were several strongly positive L. E. preparations, and the electrocardiogram had a right bundle-branch block. X-rays and fluoroscopy showed markedly limited diaphragmatic motion. The patient's hospital course was downhill, with joint effusions, peripheral neuropathy and dyspnea increasing until death.

* One, New York Hospital; one, Montefiore Hospital.

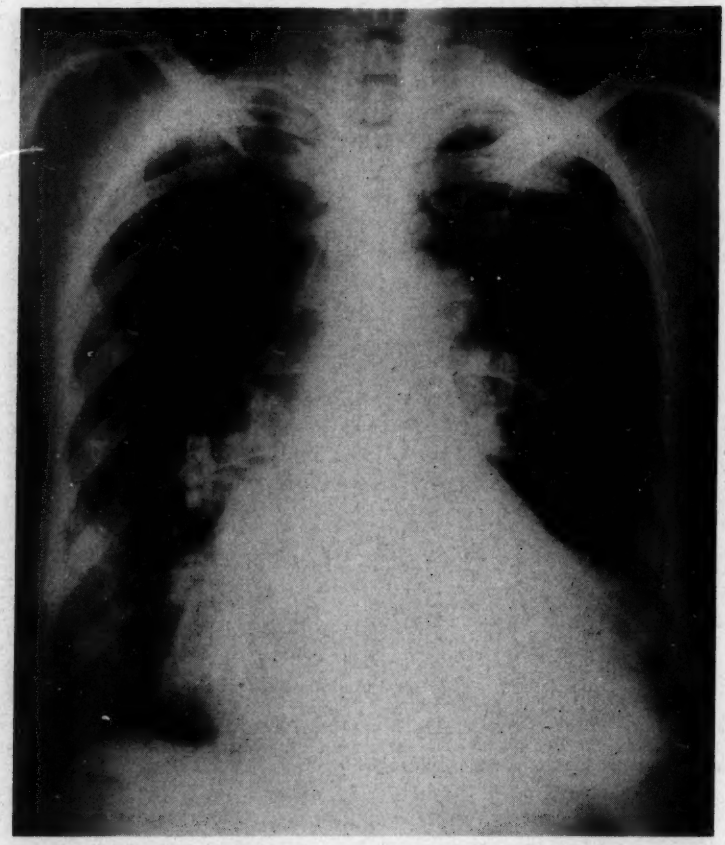

FIG. 2A. A 58 year old female presented left flank-chest pain, pleuritic in type, two months before admission. There had been no other evidence for S. L. E. until admission on April 2, 1955, when x-ray showed only a large heart and some congestion. The present film (4/4/55) shows the appearance of pleural reaction, left costophrenic angle, confirmed on lateral view and by removal next day of 50 c.c. (only) of pleural fluid.

Autopsy revealed adhesions of the pleura, pericardium and peritoneum; multiple joint synovitis, dilatation and hypertrophy of the right heart. Microscopically, however, there were no lesions typical of lupus. The *kidneys* showed some increased interstitial connective tissue and, in the small vessels, thickening of the walls with endothelial proliferation.

In the other case there were diffuse interstitial pulmonary fibrosis, nonspecific node enlargement, plasmacytosis and other changes "consistent" with S. L. E. No further diagnosis was possible.

Four of the clinically diagnosed cases of "S. L. E." which came to autopsy did not fulfill our "four points," and none showed definite lupus at autopsy.

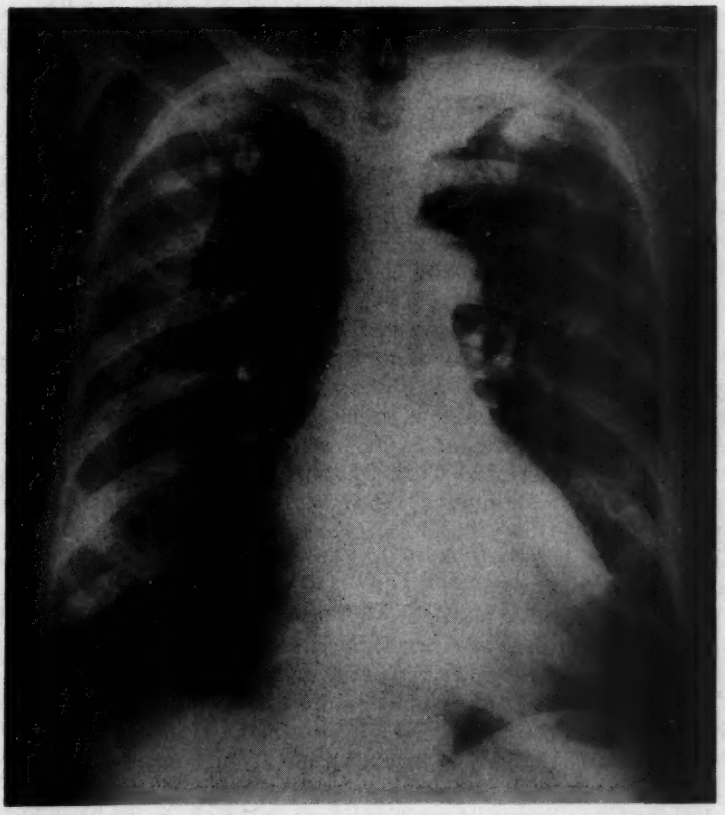

FIG. 2B. Cortisone was begun on April 6, 1955. Film (4/15/55) shows complete clearing of pleuritis. Patient died a year later, autopsy confirming S. L. E.

One had healed rheumatic heart disease and chronic interstitial and glomerular nephritis; another showed diffuse interstitial pulmonary fibrosis; in the other two, no definite diagnosis was possible.

DISCUSSION

A comparison of our results with those of others (tables 1 and 3) reveals that a higher proportion of our cases had pleuritis (41, or 72% of those whose x-rays were seen) than was found in any other series save that of Gould and Daves. Also, our figure of 46% with frank effusion was exceeded by no one save Dubois. The higher incidence may be explained by our selection of only rigidly proved cases of S. L. E., which tend to be diagnosed in the last stages of the disease where pleuritis is most frequent.

However, this means the data on timing of the pleural involvement are all the more striking. Of the 57 cases in table 3, 14 (24.6%) had definite pleuritis, symptomatic and demonstrable by x-ray, before they had shown more than one other major and one minor symptom of S. L. E., i.e., before the diagnosis was at all clear. Five additional patients had typical pleuritic pain early in their disease, although x-rays (not done until after the acute episode) showed no clear traces of the lesion. Four of these developed x-ray pleuritic changes later.

That many of these episodes cleared rapidly and completely, with or without treatment, is in keeping with Tumulty's [44] observation. In this regard, the pleura behaves somewhat as if it were a peripheral rather than a visceral organ. Pleuritis, moreover, usually causes specific and dramatic pain, and when x-ray changes are added, in the absence of pneumonitis, the differential diagnosis begins to narrow. In contrast to the other signs of S. L. E., such as arthritis, carditis, nephritis, pneumonitis, fever, or even pericarditis, there are very few other probable causes for this syndrome, aside from tuberculosis or neoplasm. Only a typical "butterfly rash" is a more specific indication for an intensive search for lupus. When another sign, such as arthritis or rash, is detected, the diagnosis of S. L. E. must be most strongly considered.*

Unlike those cases described in the Introduction, none of this series showed proved lupus pleuritis as the only initial sign. However, three of the 57 patients had true pleuritic pain before any other major symptom of lupus. For two of these, the first x-ray revealed pleuritis but, in the meantime, one or more of the other signs of S. L. E. had appeared.

In general, our data on symptoms preceding pleuritis (table 4) agree with those in the literature. S. L. E. is believed to be rather rarely preceded by "discoid lupus." [3b] Our finding of only eight cases with early skin involvement, as opposed to 22 with arthritis or arthralgia, is in accord with this belief. The absence of false-positive serologic tests for syphilis often noted as an early sign, may be due simply to the retrospective method of study. The absence of pericarditis and the single mention of renal disease seem significant in stressing the grave prognosis and usually late occurrence of these signs.

In our method of determining "pleuritis," the criteria of Gould and Daves were mentioned. They [13] describe intensive search for minimal changes: blunting or mere "pinching" of costophrenic angles, lateral displacement of mediastinal pleural reflection, forward displacement of posterior visceral pleura, and shaggy irregularities along the lateral chest well.† We were unable to detect any such fine changes with certainty. We therefore feel that the pleuritis included here would be detected by the general practitioner with no more than a good posteroanterior and lateral film, plus the history.

* Compare with findings of Emerson [10] and others regarding remote possibility of pleuritis in rheumatoid arthritis.

† Daves, M. L.: Personal communication.

Summary and Conclusions

1. Pleuritis, with and without effusion, is common in S. L. E. Among 57 consecutive proved cases it was found in 41, seven of whom had other pleural disease. It was recorded in 10 of 20 additional cases whose x-rays were unobtainable.

2. Pleuritis is often an early sign of S. L. E. In three of the 57 cases it appeared as an isolated first sign. In 16 more it appeared with few antecedent symptoms of S. L. E.

3. Despite this frequency of early pleuritis in S. L. E., sufficient weight is rarely given this disease in the differential diagnosis of "idiopathic pleuritis."

4. By far the most striking antecedent symptom of S. L. E. was arthritis or arthralgia. The only closely associated lesions were pneumonitis and pericarditis, but with a lesser frequency than had been noted by other observers.

5. Pleuritis in this series was often followed by complete clearing. Of the 39 uncomplicated cases followed by x-ray, 14 cleared one or more episodes completely, and eight cleared save for minimal pleural residua.

6. Survival following the first pleuritic episode averaged 39.9 months, with 23 of the 42 patients still alive at last follow-up.

7. Bilateral (simultaneous or alternating) pleuritis was seen in 23 out of the 42 uncomplicated cases. Of the 19 remaining, 13 were left-sided.

8. Despite the tendency to frequent infections in S. L. E., it was possible to rule out infectious, neoplastic and metabolic causes of the pleuritis in the majority of cases.

9. Criteria for the diagnosis of S. L. E. in life are mentioned and appear justified in 23 of 24 autopsied cases.

10. In view of the increasingly favorable results of therapy in S. L. E., not only symptomatically but also in objective life prolongation,[9] the prompt study of cases with unexplained pleuritis is urged for S. L. E. as well as for tuberculosis or neoplasm.

Acknowledgment

Our thanks to Dr. John A. Evans, Chief, Department of Radiology, New York Hospital, and Dr. Robert Bloch, Chief, Division of Pulmonary Diseases, Montefiore Hospital, for their encouragement and kind advice in the preparation of this manuscript.

Summario in Interlingua

Es presentate un studio retrospective que comprende 77 demonstrate casos consecutive de systemic lupus erythematose. In 57 le roentgenogrammas esseva revidite. Le remanente 20 esseva studiate solmente super le base del graphicos hospitalari. Pleuritis—con o sin effusion—esseva trovate in 41 del 57 casos con roentgenogrammas e in 10 del 20 alteres. In le gruppo a roentgenogrammas, tres casos habeva manifestate pleuritis como isolate signo primari de systemic lupus erythematose, e in 16 altere casos del mesme gruppo, pleuritis appareva in association con pauc symptomas antecedente de systemic lupus erythematose.

Un revista del litteratura revela un alique plus basse incidentia de pleuritis in le majoritate del series publicate e non plus que sparse informationes relative al tempore del declaration del pleuritis in relation al altere signos de systemic lupus erythematose. Es suggerite que le tendentia de reguardar pleuritis como un signo tardive de systemic lupus erythematose resulta del difficultate de establir un diagnose precoce del morbo subjacente. Es etiam exprimite le opinion que le test del cellulas "L.E."—per render possibile plus prompte diagnoses—augmenta simultaneemente le numero del casos in que pleuritis es constatate in association con systemic lupus erythematose in su phases precoce.

Inter le symptomas a datas anterior al pleuritis, per multo le plus frappante esseva arthritis o arthralgia. Quanto al symptomas de occurrentia simultanee con pleuritis, le sol correlation significative concerneva pneumonitis e pericarditis, e le incidentia de iste duo esseva inferior a illo notate per le majoritate del altere observatores. In le presente serie, como in alteres, il habeva un tendentia marcate de progreder rapidemente al clarification del episodios pleuritic. Le 39 non-complicate casos in que roentgenogrammas esseva examinate includeva 14 con clarification complete de plure episodios de pleuritis e octo alteres con persistentia de solmente minimal residuos. Le superviventia medie post le prime episodio pleuritic esseva 39,9 menses (con 23 ex 42 patientes ancora vive al tempore del plus recente revista).

In le presente serie—de accordo con alteres—le affection pleural tendeva a interessar ambe lateres (in alternation o simultaneemente). Isto valeva pro 23 del 42 non-complicate casos. Inter le remanente 19, le latere interessate esseva 13 vices le latere sinistre.

Le diagnose de systemic lupus erythematose continua presentar considerabile difficultates, mesmo al necropsia. In duo de nostre 24 casos con necropsia, le constatationes post morte sol haberea essite dubitose. Tamen, es presentate criterios pro le diagnose in vivo, e iste criterios esseva observate strictissimemente in le presente serie. Le assertion que nulle signo de systemic lupus erythematose poteva esser trovate al necropsia valeva definitivemente in non plus que un sol caso, e in isto il se tractava de periarteritis nodose.

Viste que systemic lupus erythematose comporta un predisposition al contraction de infectiones, il es probabile que certes del casos de pleuritis reportate esseva de character infectiose e non causate per systemic lupus erythematose per se. Tamen, in le majoritate del casos iste possibilitate esseva excludite. Le mesmo es ver pro causas neoplastic e cardiac.

In consideration del facto que le resultatos therapeutic obtenibile in systemic lupus erythematose es progressivemente plus favorabile, le presentia de ille condition deberea esser investigate in omne casos del si-appellate pleuritis idiopathic.

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RHEUMATOID SPONDYLITIS: MANIFESTATIONS AND MANAGEMENT *

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RHEUMATOID spondylitis is one of the most common arthritic diseases affecting young and middle aged men during their most productive years and, with the exception of trauma, is probably one of the most common causes of backache in this segment of the population. Its importance as a cause of morbidity and disability in young men is attested to by the numerous articles [1-8] which appeared in the medical literature during the war years and thereafter. However, despite this keen interest, the disease in many patients is unrecognized during its early stages and is allowed to progress until irreversible deformities develop before the correct diagnosis is made and proper management for its control is instituted. It appears, therefore, that some aspects of this disease need further clarification, especially in regard to its earlier recognition and to the institution of proper and effective therapeutic measures.

METHODS

The records of 267 patients in whom the diagnosis of rheumatoid spondylitis was made were carefully reviewed. Some of the available data pertinent to this study are indicated in table 1. With few exceptions, all patients were examined and treated by one of us (A. M. L.). Since this study was made at a Veterans Administration hospital, where the majority of patients are males, all these patients were of that sex. The diagnosis

TABLE 1

Clinical Features

	Number of Patients	Per Cent
Family history of arthritis	25 of 201	12.4
Trauma	66 of 229	28.8
Subjective complaints of arthritis in peripheral joints	166 of 264	62.8
Objective signs of arthritis in peripheral joints	113 of 266	42.4
Radiographic changes in sacro-iliac joints	267 of 267	100.0
Radiographic changes in hip joints	41 of 267	15.3
Calcification of ligaments	89 of 267	33.3
Osteoporosis	64 of 267	23.9

* Received for publication June 4, 1957.

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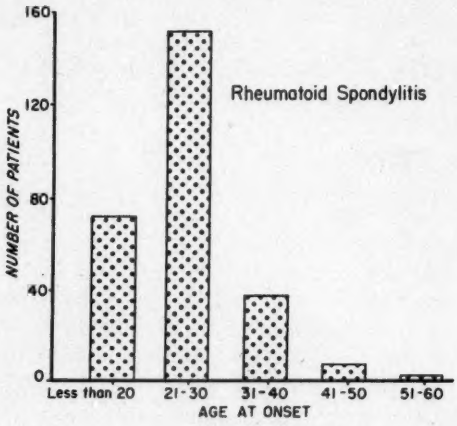

FIG. 1.

of rheumatoid spondylitis in every instance was made on the basis of the history, physical findings and radiographic evidence. Roentgenographic examination included A-P and lateral views of the lumbosacral, dorsal and cervical spines. Whenever indicated, special inclined views of the sacroiliac joints and oblique views of the lumbar and cervical spines were obtained. Blood studies included the following determinations: hemoglobin, white blood cell count, erythrocyte sedimentation rate and, in a few patients, C-reactive protein, total serum proteins, albumin, globulin and A/G ratio. The results are shown in table 2. Treatment consisted of physiotherapy, irradiation of painful areas of the spine, instruction in breathing and postural exercises, measures of rehabilitation, dietetic management, correction of

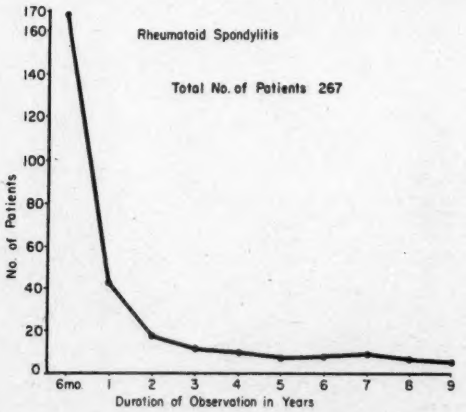

FIG. 2.

static factors, braces, aspirin and, in a few patients, hydrocortisone and Butazolidin. During the later period of this study only those patients were treated with irradiation of the spine who failed to respond to the other measures.

Observations

The age at onset (figure 1) of the disease varied from the second to the sixth decade; the youngest patient was 17 years and the oldest 54 years at the onset of the disease. The period of observation (figure 2) varied from a few months to as long as nine years. The greatest number, 153 (57.4%), were in their third decade at the time of onset of the disease (table 3). In 201 patients the presence or absence of arthritic disease in the family was recorded; of these, 25 (12.4%) gave a history of "arthritis" in some other member of the family. Trauma was given as a precipitating

Table 2

Laboratory Data

	Hemoglobin				White Blood Cell Count			E.S.R. (Wintrobe Method)	
Gm. %	>14.5	>13.5	>10.0	<10.0	>10,000	>5,000	<5,000	>10 per hr.	<10 per hr.
No. of pts.	117	70	60	9	57	190	14	209	46
Per cent	45.7	27	23.4	3.5	21.8	72.8	5.3	81.9	18

	C-RP		Total Serum Protein		Albumin (Normal 3.0–4.5 gm. %)		Globulin (Normal 2.3–3.6 gm. %)		Reversal A/G Ratio
	Pos.	Neg.	Normal	Abnormal	Normal	Decreased	Normal	Elevated	
No. of pts.	23	3	35	0	32	2	25	9	7

factor by 66 (28.8%) of 229 patients. Subjective complaints of peripheral joint involvement were present in 166 of 264 (62.8%); objective signs of peripheral joint involvement in 133 of 266 (42.4%); and sciatic radiation in 63 patients (23.5%). All patients had radiographic evidence of sacroiliac involvement. Calcification of the vertebral ligaments was present in 89 patients (33.3%), and osteoporosis in 64 patients (23.9%). Forty-one patients (15.3%) had hip joint involvement. These data are recorded in table 3, and graphs.

Mode of Onset

The onset of the disease in the majority of the patients was insidious, generally over a period of several months or even years, and progression of the disease was interrupted by pain-free periods lasting several weeks or months. With each relapse, however, the symptoms were generally more severe and the duration of each episode was longer; ultimately the symptoms

TABLE 3

Age at Onset, and Duration of Observation

Age at Onset	Number of Patients	Duration of Observation	Number of Patients
Less than 20	71	Less than 6 months	168
		More than 1 year	41
21–30	152	More than 2 years	17
		More than 3 years	11
31–40	37	More than 4 years	10
		More than 5 years	4
41–50	6	More than 6 years	5
		More than 7 years	6
51–60	1	More than 8 years	2
		More than 9 years	3
Total number patients	267	Total number patients	267

became more or less constant. Thus, there was a gradual increase in the severity of the patient's complaints. In a small number of patients the course of the disease was progressive and developed fairly rapidly, although they continued to have periods of exacerbations and remissions. The most common symptoms at the onset of the disease were stiffness and aching in the low back in the morning on awakening which would persist for half an hour or longer. With activity, the back would "limber up" and the aching and stiffness would gradually disappear toward the late forenoon, only to return toward the end of the day or during the night while the patient was lying in bed, awakening him. The severity of the backache varied considerably in different patients. Characteristically, it awakened the patient two or three hours after falling asleep. The patient would then get off the bed and walk about for one-half hour or longer to obtain relief; then he would return to bed, only to be awakened again in two or three hours, to repeat the process of walking to obtain relief. Patients whose disease was more severe repeated this process two to three times nightly, so that their rest and sleep were markedly disturbed and, as a result, their general well-being suffered, their appetites became poor, and they lost weight. In some patients numbness of the lower extremities accompanied the aching and stiffness in the low back, and they "had to rub" their lower extremities to obtain relief. In many patients the disease began as "catches, like pinching of a nerve" in one or the other hip region, at times radiating anteriorly to the iliac crests or abdomen. A few patients complained of weakness, or a sensation of "giving way" of the hip, alternating from one to the other hip. Radiation of pain to the buttocks, groins or along the posterior or, less often, the lateral aspect of the lower extremities to the knees or ankles occurred in some patients and, in a few, tingling in the toes on walking. In some, the backache was aggravated on coughing, sneezing, lifting weights or on any movement of the spine. The aching in the back at times was so severe that it seemed to "double up" the patient. A few subjects stated that the backache

was accompanied by a tightness or "knot" in the abdomen, spasmodic contractions and rigidity of the abdominal musculature. Patients with involvement of the dorsal spine complained of soreness or migratory sharp pains in the chest during respiration and yawning, and had varying degrees of impaired chest expansion. The complaints were generally worse after periods of inactivity and, in some patients, during inclement weather. A few patients dated the onset of aching and stiffness in the low back to a time when they were treated in a hospital for some other apparently unrelated disease, such as gunshot wound, tonsillitis, etc. Three patients had been explored surgically for herniation of the nucleus pulposus at other institutions prior to our observation. A small number of patients had been believed to be psychoneurotic before the nature of their complaints was recognized, the correct diagnosis made and proper therapy instituted. In contrast, a few patients had only minor complaints referable to the spine, despite well developed deformities and advanced radiographic changes. These patients were generally older men in whom the disease was accidentally discovered while they were in the hospital for the treatment of an unrelated condition, such as hypertension, coronary artery disease, pulmonary emphysema, etc. Careful questioning of these patients revealed that in the past they had had only temporary discomfort in the back, consisting of aching and stiffness which did not interfere with the pursuit of their occupation or customary activities.

Physical Findings

There was considerable variation in the objective findings. In the milder cases, during the early stages of the disease, no abnormal physical findings were noted and, as a rule, no abnormalities were seen on the radiograms. These were diagnosed on subsequent admissions to the hospital when definite objective abnormalities were found and radiographic evidence of the disease developed. In these instances we found the various leg and spinal maneuvers, particularly Lasègue's, Patrick's, Gaenslen's and Ely's, and extent of chest expansion, of great help in arriving at the correct diagnosis.* Patients in whom the disease was more advanced presented some or all of the following manifestations in different degrees of severity: flattening of the lumbar spine, with partial or complete obliteration of the normal lumbar lordotic curve and exaggeration of dorsal kyphosis; flattening of the chest and impaired chest expansion; tenderness on pressure or percussion

* *Lasègue's Maneuver:* Flexing the extended lower extremity upon the abdomen and noting the angle of flexion at which the pain in the low back is reproduced.

Patrick's Maneuver: With the patient in the supine position, the leg and thigh are flexed and the lower extremity is abducted and externally rotated at the hip.

Gaenslen's Maneuver: Hyperextension at the hip of the extended lower extremity while the opposite lower extremity is forcibly held by the patient in the knee-chest position.

Ely's Maneuver: With the patient in the prone position, the leg is flexed on the thigh and the lower extremity is hyperextended at the hip.

Chest Expansion: The circumference of the chest is measured at the level of the nipples at the end of full inspiration and expiration.

over the sacro-iliac joints and vertebral column; varying degrees of atrophy of the muscles of the spine; rigidity and impairment of some or all spinal movements; anterior fixation of the cervical spine; forward crouching deformity of the entire vertebral column, the so-called "poker spine"; and "en masse" movement of the entire spine. One patient had such marked anterior flexion and rigidity of the vertebral column that the longitudinal axis of the head was parallel to the floor. Several patients who had involvement of the hip joints had a characteristic waddling gait, walking with slightly flexed knees, forward-bent body and hyperextended neck, the upper extremities swinging in a plane posterior to that of the body as they shifted the pelvis from side to side with each step.

Laboratory Data

Nine patients (3.5%) had less than 10 gm.% hemoglobin; 130 patients (52%) had mild to moderate decrease of hemoglobin concentration, and 117 patients (45%) had normal levels of hemoglobin. The white blood count was more than 10,000 per mm.^{3} in 57 patients (21.8%); the highest count was 16,400; 14 patients (5.3%) had counts of less than 5,000 per mm.^{3}; the lowest count was 3,200; 190 patients (72.8%) had normal white cell counts. The erythrocyte sedimentation rate was normal in 46 (18%) and abnormally elevated in 209 patients (81.9%); the highest level was 54 mm. in one hour. The C-reactive protein was determined in 26 patients; it was positive in 23 (88.4%) and negative in three patients. The total serum protein level was normal in all 35 patients in whom it was determined. The levels of the albumin and globulin fractions were determined in 34 patients. The level of albumin was normal in 32 and below normal in two patients; the globulin fraction was normal in 25 and abnormally elevated in nine patients; the highest level of globulin was 4.9 gm.%. The albumin-globulin ratio was reversed in seven patients (table 2).

Radiographic Changes

It is generally known that the subjective manifestations of rheumatoid spondylitis may make their appearance long before definite evidences of the disease are seen in the radiograms of the sacro-iliac joints and/or of the spine.[1] This interval may vary from a few months to a few years. A still greater difficulty is the recognition and correct interpretation of the early radiographic changes caused by the disease in the sacro-iliac joints, and particularly in the small diarthroidal joints of the vertebral column, namely, the apophyseal, the costovertebral and costotransverse articulations. The differentiation of these minor changes from the normally occurring variations in the size, shape and direction of the articular facets is extremely difficult.[9-14] We obtained considerable help from inclined views of the sacro-iliac joints taken with the x-ray tube tilted at an angle of approximately 35°,

and oblique views of the lumbar and cervical spines. The inclined views of the sacro-iliac joints render clearer visualization of their margins and joint spaces, so that minor changes could be differentiated more readily from the normally occurring variations.

All patients had radiographic evidence of involvement of the sacro-iliac joints. These changes were varied: narrowing or widening of the joint spaces, irregular and indistinct joint margins, at times serrated edges, partial or complete obliteration of the joint spaces, spotty osteoporosis and irregular sclerosis of the adjacent sacrum and/or ilium. Similar abnormalities were noted in the apophyseal joints of the lumbar spine and the cervical spine. Adequate or correct recognition of such changes in the dorsal spine was rarely possible because of interference by overlapping rib shadows. Calcification of spinal ligaments was recognized in 89 patients (33.3%). The degree and extent of calcification also varied markedly; in some, it was present only in two or three isolated areas of the spine irregularly spaced; in others, it involved all the ligaments, produced the characteristic "bamboo effect," and transformed the entire spine into a rigid column. The hip joints were involved in 41 patients (15.3%); the abnormalities consisted of varying degrees of narrowing of the joint spaces, erosions of the cortices of the head of the femur and acetabulum, spotty osteoporosis, and irregular areas of sclerosis in the head of the femur and acetabulum.

In a few patients the margins of the symphysis pubis showed considerable irregularity and spotty osteoporosis of the adjacent bones. Irregularities of the lower margins of the ischia, spotty sclerosis and osteoporosis of the adjacent bones were also occasionally present. Osteoporosis of the entire spine was noted in 64 patients (23.9%).

Associated and Interesting Manifestations

Three patients presented the triad of Reiter's syndrome, i.e., urethritis, iritis and arthritis involving both the spine and some of the peripheral joints. One patient had complete ankylosis of the temporomandibular joints and was unable to separate his jaws sufficiently to permit the intake of solid food. The condyles of the mandible were resected. Ankylosis recurred several months later; it was then relieved by arthrotomy and replacement of the condyles by Vitallium prostheses. Thirteen patients (4.5%) had iritis or iridocyclitis; six of these had involvement of the peripheral joints also. Five patients (1.8%) had psoriasis; all had involvement of the peripheral joints also. Thirty-six (13.5%) had various forms of anomalies of the spinal column; these are indicated in table 5.

Diagnosis

Rheumatoid spondylitis is easily recognized in patients in whom the disease is well developed. During its early stages, however, the diagnosis

TABLE 4

Response to Therapy

	Number of Patients	Response				% Good or Excellent	
		None	Fair	Good	Excellent		
Physiotherapy	95	4	21	52	18	73.7	
Radiation							
One course	116	13	17	57	29	74.1	Mean
Two courses	42	1	8	23	10	78.5	75.5%
Three courses	7	0	1	3	3	85.7	
Total	260	18	47	135	60	75.0	

is often difficult. When objective manifestations of the disease, or corroborative radiographic changes, are lacking, the fatigability, weight loss and inconstant pain in joints or muscles of the spine are usually ascribed to psychogenic factors. Since there are no specific diagnostic tests, it is often impossible to arrive at the correct diagnosis until characteristic signs of the disease or abnormal radiographic changes appear. We found the following of considerable value in diagnosing the disease: (1) aching in any part of the back in a young man which occurred often during the night and induced him to get off the bed to "limber up"; (2) careful evaluation of results of leg and spinal maneuvers, and particularly the flexibility or rigidity of the spine on body movements; (3) meticulous examination of x-rays of the sacro-iliac joints, and especially of the inclined views of these joints. The laboratory data were of limited value in diagnosing the disease. The erythrocyte sedimentation rate and C-reactive protein were elevated in the majority of patients. The hemoglobin level was slightly to moderately decreased in approximately half of the patients.

MANAGEMENT

Seven patients were asymptomatic at the time of observation and needed no therapy. The remaining 260 patients were treated with a variety of therapeutic measures. The complaints and findings of each patient were carefully considered prior to outlining his therapeutic regimen. Boards

TABLE 5

Associated and Interesting Manifestations

Reiter's syndrome	3
Iritis	13
Psoriasis	5
Anomalies of Vertebral Column	
Transitional lumbosacral joint	15
Spina bifida occulta	8
Spondylolysis	6
Spondylolisthesis	3
Miscellaneous	4

were placed under the mattress to prevent sagging of the bed, and the patient was advised to use no pillow under his head while lying in the supine position. Pillows were used under the head when the patient was lying on his side; they were also used under the lumbodorsal spine while lying in the supine position, or at some level under the trunk while lying in the prone position, provided such positioning of the pillow added to his comfort. Static factors such as tilting of the pelvis, inequalities in the length of the lower extremities or weak feet were corrected by construction of heel lifts, metatarsal bars, arch supports, etc. Dental care was given. Instruction in deep breathing and in exercise to correct postural abnormalities and to strengthen the muscles of the back and abdominal wall was given. Appropriate dietetic management was prescribed, i.e., patients who were underweight were given a high calorie and high protein diet (approximately 3,000 calories containing 100 to 150 gm. of protein daily), and overweight patients were placed on a reducing diet (800 to 1,200 calories). Dry or moist heat (infrared, diathermy, hydrocollator pack) was applied locally to the painful regions of the spine and to the involved peripheral joints. Ultrasound was applied in some instances. Occupational and corrective therapy was employed. When present, synovial fluid was aspirated in peripheral joints, and hydrocortisone, 25 to 50 mg., was injected intra-articularly whenever this was deemed advisable. Aspirin, 0.3 to 1 gm. at four-hour or longer intervals, was used to control pain whenever needed. A few patients who complained of severe pains in the chest and abdomen of radicular distribution, or had spasm of the abdominal and intercostal muscles, were given hydrocortisone orally (50 to 100 mg. daily in divided doses), or phenylbutazone (400 to 600 mg. daily) for short periods of time. Radiation therapy * was administered with the Maximar 250 Kv or the Picker 200 Kv unit to painful areas of the spine through one to five portals in doses of 150 to 200 r as measured on the skin or air on alternate days for a total dose of 600 to 750 r to each area. The size of the portals over the sacro-iliac joints was 10 by 12 cm., and over the spine, 6 by 12 to 6 by 15 cm. The following factors were employed.

Filter—Thoreaus No. 2 or 0.5 mm. Cu and 1 mm. Al.
HVL—1 or 2 mm. of Cu.

If symptoms persisted, a second course of radiation therapy consisting of 450 to 600 r through each of two to five portals was given at an interval varying from six weeks to several months. A few patients were given a third series, several months later, consisting of 300 to 450 r through each of one to three portals. No serious toxic reactions were observed from irradiation. A number of patients complained of nausea and occasional vomiting, and a few had a moderate degree of leukopenia. The leukopenia

* Radiotherapy was administered under the supervision of Dr. Ralph Braund, Dr. Walter Mendel and Dr. Benjamin Greenberg.

was temporary. The nausea and vomiting were relieved by Dramamine in doses of 50 mg., or Bonamine in 25 mg. doses.

Most patients whose radiograms showed osteoporosis were placed on a so-called "osteoporotic regimen" for a period of three weeks. This regimen consisted of the following: (1) high calorie, high protein diet; (2) ascorbic acid, 100 mg. orally, daily; (3) depo-testosterone, 25 mg. intramuscularly, three times weekly; (4) stilbestrol, 1 mg. orally, daily; (5) vitamin B_{12}, 100 μg intramuscularly, three times weekly. Sixty-three patients were fitted with braces (Taylor, three-point, Knight or von Wersowitz) to support the lumbodorsal spine. Plaster body casts with wedging or turnbuckles were employed in a few patients in an attempt to correct extreme forward-crouching deformities. Three patients had arthrodesis or arthroplasty of one or both hip joints. One patient had bilateral arthroplasty of the temporomandibular joints to relieve ankylosis of these joints, and one patient had arthrotomy and synovectomy of the left sternoclavicular articulation.

The nature of the disease in the light of presently held views was explained to the patient, with assurance of its generally benign character and eventual "burning out" of activity. The patient was encouraged to maintain an optimistic outlook. Emphasis was placed on the importance of maintaining good posture to prevent the development of deformities, of continuing muscle strengthening and breathing exercises, of the use of physiotherapeutic measures at home, and of the necessity of avoiding overexertion and upper respiratory tract or other infections. He was also advised to shift his position at sufficiently frequent intervals to prevent too great a "jellying" effect, to avoid bending over or lifting heavy objects, to bend his knees as in stooping, instead of bending his spine, when lifting objects off the floor, tying shoelaces, etc., and to avoid postures or activities that aggravated his discomforts. An attempt, not always successful, to rehabilitate the more severely affected patients was made by giving them vocational guidance and assistance in changing to an occupation which did not involve standing or sitting for prolonged periods, or arduous physical exertion.

Results

It was difficult to evaluate the results of therapy correctly in terms of arrest of the disease, or the extent of relief of the subjective complaints. Duration of hospitalization could not be used as an indicator because many of our patients remained in the hospital for reasons other than their complaints referable to the spine. In estimating the effect of therapy, we relied generally on the degree of lessening of subjective complaints, especially decrease or disappearance of aching and stiffness, and extent of freedom of body movements. The degree of improvement was expressed as: (1) excellent: complete relief of subjective complaints and ability to resume regular occupation; (2) good: considerable relief of subjective complaints and

ability to carry out body movements with relative freedom; (3) fair: some decrease of aching and stiffness; (4) no effect. The results are indicated in table 4.

It is seen that "good" or "excellent" response was noted in 70 of 95 patients (73.7%) who were not given irradiation therapy, and in 125 of 165 patients (75.7%) who were given one to three courses of irradiation. There is therefore no significant difference between the two groups. We must emphasize, however, that the comparison is not valid because: (1) irradiation was only one of several therapeutic measures employed in the management of our patients, and (2) we did not evaluate separately the efficacy of physiotherapeutic measures apart from irradiation therapy. Our aim was to employ a therapeutic regimen which would expeditiously bring about a satisfactory remission of the disease and maintain this remission as long as possible.

Discussion

During the course of this study we were impressed by the variability of the subjective manifestations and the general lack of correlation between subjective complaints, clinical manifestations, alleged disability and the roentgen manifestations, especially during the early stages of the disease. We became aware of the influence of the expected gain to be derived from the persistence of complaints in regard to awards of disability compensation in many of our veteran patients. Nevertheless, the diagnosis could be made with certainty in most of these patients. We found the following clinical features to be of value in diagnosing the disease during the early stages: (1) the complaint of aching and stiffness in any part of the lumbodorsal spine, occurring during the night, awakening the patient two to three hours after he had fallen asleep, and necessitating his getting off the bed and walking around in order to "limber up" and obtain relief; (2) the repetition of this process two to three times nightly; (3) the occurrence of stiffness and aching in any part of the lumbodorsal spine on awakening in the morning, but "limbering up" upon resumption of activity; (4) reaction of the patient to the performance of the various orthopedic maneuvers.

We were also impressed by the difficulty in correctly interpreting the earliest radiographic changes and their differentiation from the normally occurring variations in the margins of the sacro-iliac and apophyseal joints. We also became aware of the difficulties in estimating the extent of relief obtained separately from physiotherapy and from irradiation. This difficulty was partly due to the fact that the relief of subjective complaints occurred not infrequently two to four weeks after completion of irradiation therapy. In our experience, the best results were generally obtained from the combination of physiotherapy, irradiation, postural and muscle exercises, the judicious use of aspirin, and correction of static factors and of established deformities by orthopedic procedures.

Summary

The clinical features and roentgenographic signs in 267 patients with rheumatoid spondylitis are described. The difficulties in diagnosis encountered during the early stages of the disease are discussed, and methods found helpful by the authors in diagnosing the disease during its early stages are described. Management of the disease is discussed, and results of therapy in this series of cases are tabulated.

Summario in Interlingua

Es describite manifestationes clinic e le constatationes roentgenographic in 267 patientes mascule con spondylitis rheumatoide. Le diagnose e le tractamento es discutite. Le etates del patientes al tempore del declaration del morbo variava inter le secunde e le sexte decennio. A judicar per le gravamines subjective del patientes, affection de articulation peripheric esseva presente in 166 ex 264 casos (i.e. 62,8%). Signos objective de affection de articulation peripheric esseva presente in 113 ex 266 casos (i.e. 42,4%). In le majoritate del casos, le declaration del morbo esseva insidiose. Le grados de severitate del dolor dorsal variava considerabilemente in differente patientes. In 63 casos (i.e. 23,5%) illo esseva accompaniate de radiation sciatic e de paresthesias. In le casos characteristic, le patientes esseva eveliate per dolores dorsal duo a tres horas post addormir se. Alicunes habeva dolorose contractiones del musculos abdominal e acute dolores migratori in le thorace durante le respiration.

Le constatationes physic variava grandemente in differente patientes. Observationes frequente esseva applatation del thorace e del spina lumbar, oblitteration del curva lordotic, exaggeration de cyphosis dorsal, dysfunction del expansion del thorace, rigiditate con movimento "como massa unite" del spina integre, e dysfunction del movimentos spinal. Le nivello de hemoglobina esseva infra le norma in 55% del patientes. Le numeration leucocytic esseva normal in 72,8%. Le sedimentation erythrocytic esseva anormalmente accelerate in 209 casos (i.e. 81,9%). Vistas oblique del articulationes sacro-iliac facilitava grandemente le recognition de precoce alterationes radiographic causate per le morbo. Le alterationes radiographic in le articulationes sacro-iliac e apophysee consisteva de restriction o allargation del spatios articular, de irregular o pauco distincte margines articular, e de oblitteration partial o complete del articulationes. Evidentia radiographic de affection sacro-iliac esseva trovate in omne le casos. Calcification de ligamentos vertebral esseva presente in 89 casos (i.e. 33,3%), osteoporosis in 64 (i.e. 23,9%).

Tres patientes exhibiva le triade del syndrome de Reiter. Un patiente habeva ankylosis complete de ambe articulationes temporomandibular. Dece-tres (i.e. 4,5%) habeva iritis o iridocyclitis. Cinque habeva psoriasis. E 36 (i.e. 13,5%) habeva anormalitates del columna vertebral.

Le tractamento utilisava varie mesuras therapeutic. Factores static esseva corrigite. Le patientes esseva instruite in como respirar e como executar exercitios postural. Un appropriate regime dietetic esseva prescribite. Calor humide o sic esseva applicate al region dolorose del columna vertebral e del afficite articulationes peripheric. Fluido synovial esseva aspirate ab le articulationes peripheric. Hydrocortisona (25 a 50 mg) esseva injicite in le articulationes. Esseva utilisate therapia occupational e corrective. Aspirina (0,3 a 1 g) esseva administrate pro subjugar le dolores. Alicunes del patientes recipeva diurnemente doses oral de hydrocortisona (50 a 100 mg) o de phenylbutazona (400 a 600 mg). Patientes con osteoporosis recipeva regimes osteoporotic. Sexanta-tres esseva equipate con apparatos orthopedic.

Cento sexanta e cinque recipeva inter un e tres cursos de roentgenotherapia profunde per inter un e cinque portales dirigite a areas dolorose del columna vertebral. Esseva administrate 600 a 750 r a omne portal in le prime curso, 450 a 600 r in le secunde curso, e 300 a 450 r in le tertie curso. Cento vinti-cinque (i.e. 75,7%) obteneva bon o excellente responsas ab le irradiation. Le melior resultatos esseva effectuate per le combination de physiotherapia, irradiation, exercitios postural e muscular, uso judiciose de aspirina, e correction de factores static e de establite deformitates per mesuras orthopedic.

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ONYCHOLYSIS IN HYPERTHYROIDISM*

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OF the many clinical features of Graves' disease, alterations in the nails are probably the least frequently recognized. The late Dr. Henry S. Plummer, of the Mayo Clinic, was apparently the first to call attention to trophic changes of the fingernails in hyperthyroidism. He described longitudinal striations and flattening of the nail which, when pronounced, produce a "scoop shovel" appearance. A more striking change in the nails, however, which Dr. Plummer also described and the one with which this communication is concerned, is the condition known as onycholysis. This clinical sign has been considered pathognomonic of Graves' disease for almost four decades by Dr. Plummer's associates and students,[1] but seems to have evaded the attention of many clinicians. It is briefly mentioned in several textbooks on the thyroid.[2] The purpose of this paper is to recall to the profession the interesting phenomenon of onycholysis which occurs in some hyperthyroid patients and which is often referred to as "Plummer's nails."

Although the description of onycholysis in Graves' disease is, as mentioned, generally attributed to Dr. Plummer in about 1918, he apparently never published his observation.[3] The earliest descriptive reference is found in the chapter, "Diseases of the Thyroid Gland," by W. M. Boothby and W. A. Plummer, in *Oxford Medicine*, published in 1937. These authors credit Dr. H. S. Plummer for calling attention to the trophic nail changes and for noting that ". . . the most striking appearance is produced by the irregular separation of the soft, cutaneous structures from beneath the surface of the nail, which makes cleaning of the nails difficult and allows dirt to collect under the nail, producing a black, irregular band." [1]

The occurrence of onycholysis in exophthalmic goiter is not unusual.[4] Whereas in the healthy nail there exists a distal convexity of the curvilinear junction of the nail from its bed, there is in onycholysis a reversal of this curve, resulting from separation of the terminal central part of the nail from the bed. Thus, beneath the end of the nail an additional free space is left in which debris may collect. Uniquely, these changes occur most frequently in the fourth finger. But as the changes progress, they extend to involve

* Received for publication July 19, 1957.

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FIG. 1. A 48 year old Negro man had noted nervousness, restlessness, palpitations, insomnia and heat intolerance for 10 months. There was weight loss despite an excellent appetite. Physical findings included a blood pressure of 120/56 mm. Hg and a pulse rate of 96 per minute. The palms were sweaty and excessively warm; the skin was fine and smooth. Proptosis and lid lag were striking. The thyroid was diffusely enlarged. Radioactive iodine tracer test was in the hyperthyroid range; serum protein-bound iodine was 22 μg.% (normal range, 4.0 to 8.0 μg.%). Note moderately severe onycholysis of the fourth fingernail of the left hand, and less marked changes in the third nail of the right hand.

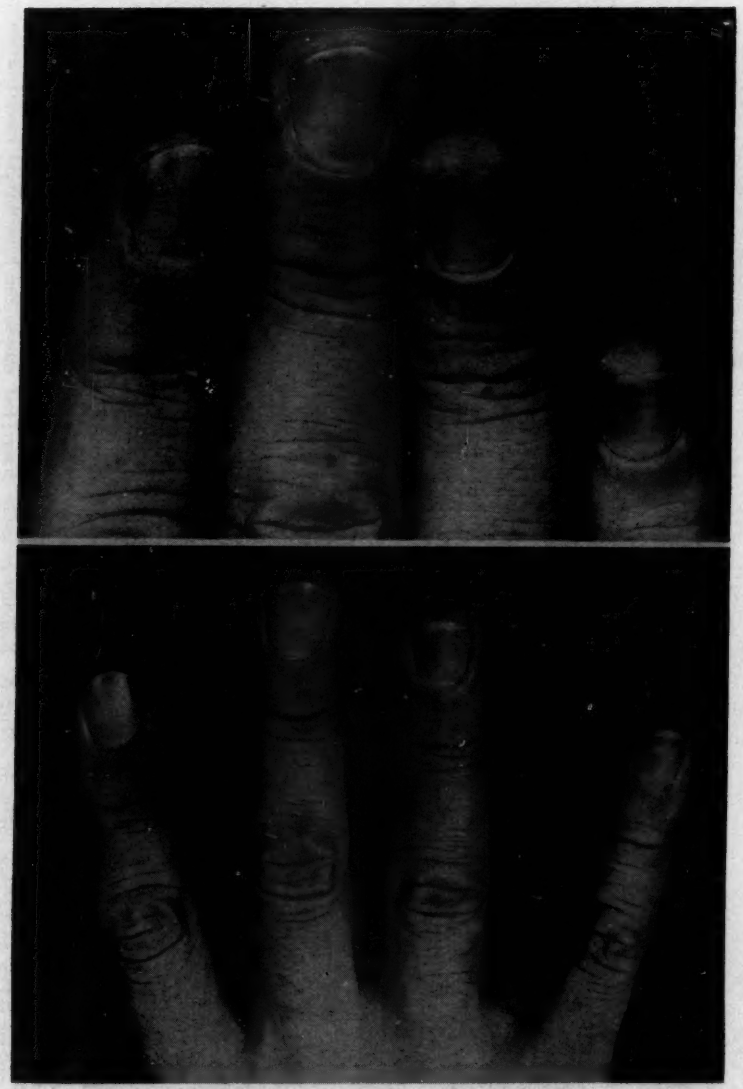

FIG. 2A (*above*). A 43 year old male clerk had experienced slight weight loss and excessive fatigue for four months. One month before examination he noted tachycardia. Findings included tachycardia and a diffusely enlarged thyroid. Basal metabolic rate was plus 36% of normal standard, and the serum protein-bound iodine level was 10.4 μg.% (normal range, 4.0 to 8.0 μg.%). Note moderate onycholysis of fourth and fifth fingernails.

FIG. 2B (*below*). Recovery from onycholysis occurred within four months in association with successful alleviation of the hyperthyroidism with methimazole therapy.

FIG. 3A. A 37 year old housewife presented with nervousness, irritability, moderate heat intolerance, tremor, proptosis and blurred vision for 11 months. Physical findings included a blood pressure of 120/60 mm. Hg and a pulse rate of 100 per minute. She had bilateral proptosis with edema of the eyelids and diplopia in all fields of vision; the left eye could not be deviated superiorly. The thyroid was diffusely enlarged. There was a slight tremor of the hands. Radioactive tracer test was in the hyperthyroid range. The nails showed minimal onycholysis of the fourth and fifth fingers of both hands.

the fifth finger, and later the remaining fingers and the thumb. Onycholysis of the toenails may also occur. The changes are depicted in figures 1–5.

In our experience onycholysis has been observed only in hyperthyroid subjects with diffuse goiter. Moreover, Haines [5] states that "undermined nails" are rarely seen in patients with hyperfunctioning adenomatous goiter. There appears to be no apparent age or sex predilection. Exophthalmos may or may not coexist. The condition improves with treatment of the hyperthyroidism, and usually disappears when the patient achieves the euthyroid state. What rôle the metabolic and hormonal derangements of hyperthyroidism play in bringing about this curious manifestation is unknown.

This sign is not pathognomonic of hyperthyroidism, since similar nail changes have been reported in patients with other systemic diseases, such as syphilis, hypothyroidism and chronic arthritis, as well as in fur workers

FIG. 3B. A normal metabolic rate was achieved in four months with methimazole treatment. Note normal appearance of nails.

FIG. 4. A 67 year old Costa Rican housewife had had a goiter for 20 years. For six years she had had difficulty in swallowing, and for several months had had nervousness, fatigue, weight loss, diarrhea, palpitations and tachycardia. Physical findings included a pulse rate of 120 per minute, soft, fine hair, diffusely enlarged thyroid (eight to 10 times normal size), and a malnourished appearance. Basal metabolic rate was plus 56%; serum butanol extractable iodine level was 16.0 μg.% (normal range, 3.2 to 6.4 μg.%). Note onycholysis of the terminal portions of all nails.

FIG. 5. A 36 year old white woman noted the onset of nervousness and irritability six months before admission to the hospital. She lost 61 pounds despite a good diet. Three months prior to admission she had developed a stare and "wide-eyed" appearance and a swelling in her neck. Physical findings included a blood pressure of 160/60 mm. Hg and a pulse rate of 130 per minute. There were proptosis, lid lag, a large diffuse thyroid and fine tremor of the hands. Basal metabolic rate was plus 84% of normal standard; serum butanol extractable iodine was 9.1 μg.% (normal range, 3.2 to 6.4 μg.%). Patient had typical onycholysis of the third and fourth fingernails.

and in persons with injured nails.[6] Yet onycholysis occurs with sufficient regularity in exophthalmic goiter that it serves as a helpful diagnostic aid.

SUMMARY

Onycholysis occurs occasionally in patients with diffuse goiter with hyperthyroidism. It usually regresses completely during or following treatment of the hyperthyroidism.

SUMMARIO IN INTERLINGUA

Onycholysis occurre a vices in patientes qui suffre de struma diffuse con hyperthyroidismo. Illo regrede usualmente e dispare completemente in le curso del tractamento pro hyperthyroidismo o como sequentia de illo.

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RENAL LYMPHATICS. III. CLINICAL IMPLICATIONS AND EXPERIMENTS OF NATURE *

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In previous publications [1, 2] the function of renal lymphatics in homeostasis of the kidney is discussed. We believe that the renal lymphatics act as a "safety valve" for the kidneys under conditions of diuresis and/or ureteral obstruction. There is experimental support for this idea.[3-6]

This collateral pathway for the escape of fluid from the kidney operates under conditions of ureteral obstruction to prevent the kidney from self-destruction. This function of the renal lymphatics may be an important factor in total renal function in a variety of diseases such as nephrosis, pyelonephritis, orthostatic albuminuria, chyluria, and possibly congestive heart failure.

In this paper several case histories illustrating pathologic conditions secondary to disease involving the renal lymphatics are presented. We feel that these conditions may have occurred as a result of failure of the renal lymphatics to serve adequately in their function as a "safety valve" for the kidney.

Case Reports

Case 1. Spontaneous Rupture of the Left Kidney.

A 76 year old white clerk was admitted to the Wadsworth Veterans Hospital on April 10, 1954, complaining of severe pain in the left flank of 18 hours' duration. He had been in good health until the night before admission, when he was suddenly seized with severe left-sided pain while watching boxing on a television program. In 1952 he had been hospitalized because of epigastric pain which occurred in relation to meals. An upper gastrointestinal series at that time was reported as normal. In that same year the patient underwent laparotomy for an attack of severe abdominal pain which was thought to be appendicitis. The appendix was found to be normal.

Shortly after the patient's admission an intravenous urogram with delayed films disclosed extravasation of opaque material about the left renal pelvis (figure 1). Because of this unexplained and unexpected finding of spontaneous rupture of the left kidney, surgical exploration was carried out immediately. At the time of operation the left perinephric area was found to be edematous and wet with escaped fluid. A small, thin area in the lower portion of the renal cortex appeared to have been the site of rupture, and a nephrostomy tube was left in place through this area.

* Received for publication July 24, 1957.

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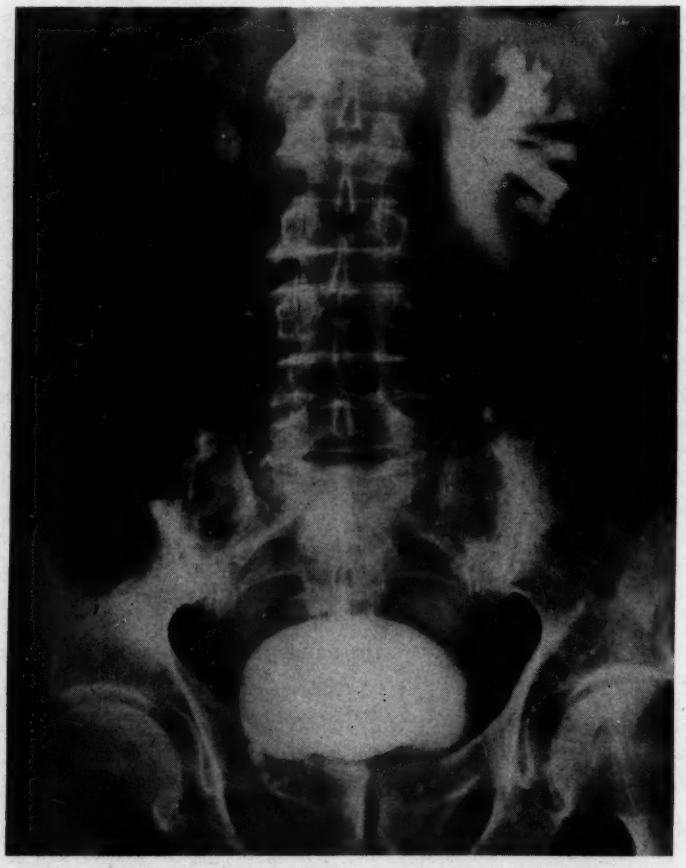

FIG. 1. *Case 1.* Intravenous urogram, showing spontaneous extravasation of contrast medium about the left renal pelvis and dilated calyces.

The renal pelvis was dilated, as demonstrated in the x-rays, and there was a kink in the upper third of the ureter which was obstructed just below the ureteropelvic junction. As a matter of routine, a small biopsy was taken from thickened periureteral tissue. The pathologist's report after microscopic examination of this biopsy was: "Metastatic adenocarcinoma, left kidney region." The primary site was thought to be the gastrointestinal tract, probably the stomach. During the postoperative period an upper gastrointestinal series demonstrated a carcinoma of the stomach. The patient continued to wear the nephrostomy tube until he died of gastric cancer two and one-half months later.

Autopsy disclosed moderate bilateral hydronephrosis. On the left side, the obstruction was due to tumor infiltration in the upper third of the ureter, and on the right side there was periureteral tumor near the bladder. An infiltrating tumor in the antrum of the stomach involved the anterior and posterior walls of the greater curvature, and lymph nodes of the gastrocolic ligament were also involved by meta-

static tumor. *The periportal, periaortic and mesenteric lymph nodes were densely infiltrated and obstructed with tumor.*

Discussion: In this case, ureteral obstruction was produced by compression from the metastatic gastric cancer, and lymphatic obstruction involving the retroperitoneal lymphatic drainage of the kidney occurred as a result of retrograde permeation from the primary carcinoma of the stomach. Ferguson [7] described a similar case, where a carcinoma of the pyloric antrum with widespread metastases obstructed the right ureter at the pelvic brim and produced spontaneous rupture of the right kidney.

Retrograde permeation of retroperitoneal and renal lymphatics from primary carcinoma of the stomach was demonstrated dramatically at autopsy by Rawson,[8] who was able with the aid of step-section technic and careful microscopic study to trace lymphatics laden with cancer cells into the substance of the kidney. By carefully mapping the area he was able to outline renal lymphatic distribution.

In the case mentioned above, and in Ferguson's case, spontaneous renal rupture occurred because of simultaneous obstruction of the ureter and the renal lymphatics by metastatic cancer. When the lymphatic "safety valve" was eliminated by obstruction, the kidney became a closed compartment and this dramatic rupture occurred.

Case 2. Spontaneous Rupture of the Kidney Due to an Obstructing Ureteral Calculus.

A 49 year old white housewife was suddenly seized during sleep with severe left flank pain. There was no nausea, vomiting, urinary symptoms or fever. She was admitted to the Cedars of Lebanon Hospital on July 9, 1954, with a tentative diagnosis of left ureteral colic. After administration of Demerol the patient became symptom-free, although the left renal area continued to be markedly tender. When an intravenous urogram was made eight hours after the onset of pain there was prompt visualization of the right upper urinary tract. On the left side, however, there was delayed excretion in the nephrogram. In delayed films, extensive extravasation around all of the fornices as well as in the peripelvic tissue of the left kidney was demonstrated (figure 2). There was dilatation of the whole left upper urinary tract down to the uretero-vesical junction, where a small calculus was obstructing the ureter. Because of the absence of fever and the subsidence of pain, expectant treatment was elected despite the disturbing appearance of the pyelogram.

The patient had no further pain, and 36 hours later she passed an irregular 3 mm. sized urinary calculus. On the following day, 48 hours after the intravenous urogram, retrograde pyelograms under local anesthesia revealed that both upper urinary tracts were normal. Even with the injection of 8 c.c. of Skiodan, no extravasation of opaque material was seen (figure 3).

The patient was discharged from the hospital and has remained asymptomatic. Six months later an intravenous urogram was entirely normal. *It is of interest that this patient gave a past history of having had a small bowel resection in 1941 for regional enteritis.*

Discussion: This case illustrates spontaneous rupture of the left renal pelvis secondary to a small calculus in the lower segment of the ureter. The pyelographic findings were strikingly similar to those in case 1.

FIG. 2. *Case 2.* Intravenous urogram showing spontaneous extravasation of contrast medium about all of the calyces and the renal pelvis. The left upper urinary tract was dilated down to the ureterovesical junction, where a small calculus obstructed the ureter.

We believe that the history of regional enteritis is significant in this case. It is likely that the retroperitoneal lymphatics were occluded or compressed by the chronic inflammatory disease, and that when the ureteral calculus produced obstruction, the renal lymphatics were unable to carry excess fluid from the kidney in the usual manner. This, as in the first case, led to a spontaneous rupture when the usual lymphatic "safety valve" was obstructed.

Case 3. Bilateral Pyelolymphatic Backflow and Multiple Renal Calculi. Cysts of the Kidney.

A 59 year old white tailor was admitted to Temple Hospital for investigation of a symptomless nodule in the prostate. Except for a history of hydrocelectomy three years earlier, the patient denied previous illness. Retrograde pyelograms were made to evaluate the upper urinary tract, and a needle biopsy of the prostatic nodule was done.[12]

Multiple tiny calcifications were seen in the kidneys, and a round filling defect, 3 cm. in diameter, was demonstrated in the midportion of the right renal calyceal pattern. Although only 4 c.c. of 40% Skiodan were injected by gravity on each side, there was clear evidence of bilateral pyelolymphatic backflow on the roentgenograms (figure 4).

Translumbar aortography [13] was performed to clarify the nature of the space-

FIG. 3. *Case 2.* Retrograde pyeloureterogram, performed 48 hours after the intravenous pyelogram shown in figure 2, and 24 hours after the spontaneous passage of the ureteral calculus. Except for a slight narrowing of the upper left ureter the pyelogram is normal, and no extravasation is noted even after overdistention of the renal pelvis.

occupying lesion in the midportion of the right kidney. The resulting roentgenogram suggested cyst rather than neoplasm. The needle biopsy of the prostate proved positive for adenocarcinoma, and on July 8, 1955, radical perineal prostatectomy was performed. Recovery was uneventful, and it was decided to reëvaluate the right renal lesion by additional pyelograms in six months.

On February 27, 1956, intravenous urography confirmed the persistence of the space-occupying lesion in the right kidney, and because of possible enlargement of this mass the right kidney was explored surgically on March 28, 1956, at Mt. Sinai Hospital in Los Angeles.

The right kidney was approached through the flank. After Gerota's fascia was opened it was evident that the perirenal fat was unusually edematous. Clear, watery fluid exuded freely from the dissected surfaces of the perirenal tissue.

Dilated lymphatics were observed in the region of the renal pedicle.

A soft area in the midportion of the kidney was punctured and 30 c.c. of clear, straw-colored fluid were aspirated from a cyst. The smooth-walled cyst was exposed

in the midportion of the kidney and found to be lined with a glistening gray membrane. Analysis of fluid recovered from this cyst showed the following:

Sugar, 106 mg.%
Total protein, 1.3 gm.%
Urea nitrogen, 31 mg.%

Urine removed from the patient's bladder at the time of surgery did not contain sugar or protein, and had a urea nitrogen content of 754 mg.%.

Discussion: This patient presents several interesting findings which may be related to stasis affecting the renal lymphatics.

There were numerous minute calcifications in the renal parenchyma which may be interpreted to be located within the renal lymphatics. Such a localization has been dramatically demonstrated by Carr,[14] who postulates that renal calculi may sometimes develop first in dilated lymphatics about the fornices, and that these lymph calculi may subsequently erode into the urinary collecting system to form true urinary calculi. He believes that lymph stasis may be one of the factors responsible for the formation of this type of minute calculus in the lymphatics.

The second interesting observation in this case is demonstration of bilateral pyelolymphatic backflow readily produced without overdistention of the renal pelvis.

The accompanying renal cyst may be of lymphatic origin similar to the peripelvic lymphatic cysts described by Berner,[15] Henthorne,[16] Scholl[17] and others. Henthorne observed that dilatation of the lymphatics of the renal parenchyma suggested the possibility that some cysts of the renal cortex are lymphatic in origin.

The multiple findings of small calcifications throughout the kidney, the pyelolymphatic backflow, a possible renal lymphatic cyst, and the presence

FIG. 4. *Case 3.* Retrograde pyelogram, performed by gravity method, using only 4 c.c. of Skiodan. Spreading of upper and middle calyces by a central space-occupying mass is seen on the right. Bilateral pyelolymphatic backflow occurred and is seen most clearly on the left.

of dilated perirenal lymphatics demonstrated at surgery, strongly suggest that some type of lymphatic obstruction was present above the renal pedicles. The history is negative for previous inflammatory disease, and there is no evidence of any retroperitoneal neoplastic process in this patient. There was also no evidence of ureteral obstruction. However, lymph stasis and lymphectasia of undetermined etiology could explain all the features noted.

Case 4. Chyluria.

A 52 year old Japanese gardener was admitted to the University Hospital on July 21, 1955, with a chief complaint of thick, whitish urine which had been occurring sporadically since 1931. Born in Japan, he had lived in the United States since 1915. In 1931 he had first noted the sudden onset of milky urine and saw a local physician, who told him that he had filariasis. There was no laboratory documentation of this diagnosis. Since that time the patient had noted that the urine became milky during the summer months, and especially after strenuous labor. He denied other urinary

FIG. 5. *Case 4.* Left retrograde pyeloureterogram, showing prominent pyelolymphatic backflow and narrowing of ureteropelvic junction. The renal pelvis was slightly overdistended by injection of the contrast medium.

symptoms. There was no evidence of lymphatic obstruction on physical examination. The urine was milky white in appearance, and loaded with red blood cells on microscopic examination. It contained "4 plus" protein and had a specific gravity of 1.023. The milky appearance of the urine cleared after the addition of ether. Serologic test for syphilis was negative. Blood urea nitrogen was 14 mg.%. Several thick smears of peripheral blood were negative for microfilariae, and a skin test for filariasis was negative. Chest roentgenograms were normal.

Intravenous urography demonstrated normal renal and soft tissue shadows and normal upper urinary tracts except for a suggestion of narrowing in the upper third of the left ureter.

On September 1, 1955, when cystoscopy and ureteral catheterization were done, milky urine was obtained from the left kidney and clear urine from the right. A left retrograde pyelogram using 30% Skiodan showed reflux of a pyelolymphatic type from the left kidney when the pelvis was slightly overdistended. The narrowing of the left ureteropelvic junction was again observed (figure 5). The right retrograde pyelogram was normal.

Later, an attempt was made to demonstrate the lymphatic connection between the retroperitoneal lymphatics and the urinary tract.* The ureters were catheterized for accurate urine collection. Fifteen cubic centimeters of sterile India ink diluted with normal saline solution were injected into the presacral retroperitoneal space as for retroperitoneal pneumography. Urine collected from each kidney through the ureteral catheters subsequently disclosed the appearance of India ink in the urinary sediment from the left kidney but not from the right kidney. The India ink appeared in strong concentration from the left side in about two hours and persisted up to about six hours. The right renal urine was clear (figure 6). There was no treatment, except dilatation of the ureteral structure. The diagnosis was chyluria, left kidney, etiology undetermined (presumably due to old filariasis).

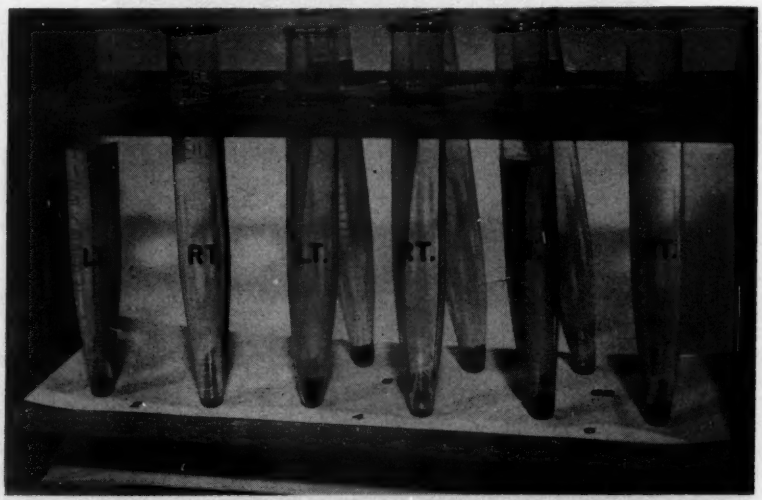

FIG. 6. *Case 4.* Split renal urine specimens obtained following the injection of India ink solution retroperitoneally. The left renal urine specimens show India ink in the sediment. Urine obtained from the right kidney contained only blood in the sediment. This study proved a urinary-lymphatic communication on the left side, but not on the right.

* These interesting studies were performed by Dr. Harry DeHaven.

Discussion of Case 4: Chyluria is generally accepted as evidence of a fistulous communication between the intestinal and retroperitoneal lymphatics and the urinary tract. It is invariably associated with lymphatic obstruction due to disease or trauma.

In case 4, unilateral left renal chyluria was dramatically demonstrated. The fact that the renal lymphatics were "open at both ends" was proved by the presence of pyelolymphatic backflow on retrograde pyelography and the rapid appearance of India ink in the urine of the left kidney after retroperitoneal injection of this material.

Lowgren [18] has studied chyluria and believes that the fistulous connection between the urinary tract and the lymphatics may occur as a result of lymph stasis secondary to lymphatic obstruction. Under these circumstances, chyle accumulates and flows in a retrograde direction. A connection is opened up with the urinary tract lymphatics in this manner. When this situation persists, one or more of the renal lymphatics ruptures and empties into the urinary tract. Yamauchi [19] believes that there is also a urinary tract obstructive element in the pathogenesis of chyluria, and that urinary stasis produces a fornical rupture, with the subsequent development of a lymphaticourinary fistula.

Lowgren has also commented upon changes in position as an influence in the appearance of chyluria. This is thought to be due to variations in the degree of compression of the lymphatics by pulling or stretching, thus influencing the passage of chyle. The appearance of chyluria associated with postural changes has also been described by Compston and Ellerker.[20]

Summary

Four cases are described in which lymphatic obstruction is thought to play a role in the development of urinary tract disease. Obstruction of retroperitoneal lymphatics may produce dilatation of the tributary renal lymphatics draining upward toward the cisterna chyli. This lymphectasia associated with lymph stasis may be related to a number of clinical problems, e.g., peripelvic lymphatic cysts, renal calculi under some circumstances,[14] and chyluria.

When complete obstruction of retroperitoneal (renal) lymphatics occurs as a result of repeated inflammatory insults or neoplastic infiltration, the kidney is deprived of an important safety valve which is necessary if ureteral obstruction occurs. In such cases (cases 1 and 2), spontaneous rupture of the fornices or pelvis or rapid destruction of renal parenchyma by unrelieved hydronephrosis or pyelonephritis may occur. Although the preceding thoughts are not proved, the clinical and experimental evidence in favor of such pathologic phenomena is very suggestive.

This provokes thought regarding the role of lymphatic obstruction in cases of ureteral obstruction, where patients are obviously toxic with ful-

minating pyelonephritis and cortical abscesses, in contradistinction to those patients who can withstand ureteral obstruction and infection with little evidence of toxicity. The rôle of lymphatic drainage of the kidney as related to tubular necrosis, hemoglobinuric nephrosis and other ischemuric states needs further elucidation.

Our laboratory and clinical observations suggest that the renal lymphatics are of importance to the function of the kidney. However, there is evidence that under certain conditions they may not be at all necessary to renal function. The work of Murray et al.[21] and Merrill et al.[22] in which prolonged functional survival of renal autotransplants and homotransplants is demonstrated, would indicate that kidneys have survived without lymphatic channels. (It is certain that lymphatic channels were transected during the surgical procedures involved.) It is conceivable that regeneration of the lymphatics may occur with renal transplantation, and that this might aid in the functional survival of these kidneys. This point should be studied and clarified.

Since Murray and his group have shown that renal autotransplants in the dog show normal response to water-loading and renal function tests, the significance of lymphatics in maintaining renal function must be seriously questioned unless regeneration of lymph channels occurs. He has shown absence of nerve regeneration in autotransplants, but lymphatic regeneration in these experiments has not been studied to our knowledge. In addition, there is no experimental work on the effects of ureteral obstruction on transplanted kidneys. Such studies in the future will help to clarify the exact significance of renal lymphatics under these conditions, and will indicate whether the deductions which we have made as a result of our experimental work and clinical observations are justified.

SUMMARIO IN INTERLINGUA

Studios experimental per le autores e per alteros ha demonstrate previemente le importantia del lymphaticos renal como "valvula de securitate" pro le ren sub conditiones de diurese e obstruction ureteral. Le rolo del lymphaticos renal in le preservation del homeostase renal ha non previemente essite recognoscite.

Le presente articulo reporta cinque illustrative casos clinic in que obstruction lymphatic es considerate como causa del disveloppamento de morbo del vias urinari. Lymphectasia secundari a obstruction del lymphaticos retro-peritonee es considerate como responsabile pro entitates del typo de peripelvic cystes lymphatic, certe formas de calculos renal, proteinuria orthostatic, e chyluria. Ruptura spontanee del fornices renal o del pelve renal e le destruction rapide de parenchyma renal per non-alleviate hydronephrose pote occurrer a vices in le presentia de complete obstruction del lymphaticos renal in consequentia de repetite insultos inflammatori o de infiltration neoplastic.

In conclusion le autores specula in re le possibilemente importante function del lymphaticos renal in conditiones del typo de nephrosis lipoide e de necrose tubular e in homotransplantation renal.

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PEPTIC ESOPHAGITIS SIMULATING THE "POST-CHOLECYSTECTOMY SYNDROME" *

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THE finding of a pathologic gall-bladder following roentgen examination has as a rule been sufficient reason for surgical intervention to relieve the patient's gastrointestinal complaints. Although removal of the diseased viscus is usually indicated, the presence of cholelithiasis or a nonvisualizing gall-bladder does not necessarily imply that the patient's symptoms are due to gall-bladder disease. The high incidence of the silent, calculous gall-bladder has been very well documented: at least 10% of a large series of patients with calculous gall-bladder were asymptomatic.[1] Occasionally, symptoms that persist following cholecystectomy are attributed to biliary dyskinesia when the intravenous cholecystogram is negative, or they may be included in that amorphous group known euphemistically as the "post-cholecystectomy syndrome." The frequency of the association of gall-bladder disease and duodenal ulcer is well known, as is the fact that symptoms are often due to the ulcer rather than to the gall-bladder. On the other hand, the association of hiatus hernia with esophagitis and gall-bladder disease has not been stressed adequately; it is not only in "elderly obese females" that the association may occur.[2] Allison [3] was among the first to point out that esophagitis may closely simulate gall-bladder disease, and that cholecystectomies have been performed without benefit because the complaints were due to peptic (reflux) esophagitis. These facts need repetition. It must be recalled that the size of the hernia is not the important factor—rather, the presence or absence of reflux, and the ease with which reflux occurs, account for the patient's symptoms. Also, the most common form of hiatus hernia, namely, the sliding hernia, is the one associated with reflux. The present report deals with four patients who have been seen recently and in whom the association of gall-bladder disease and reflux esophagitis was present. A calculous gall-bladder had been removed months or years previously but symptoms persisted. Hiatus hernia with reflux was demonstrated in each case, and esophagitis was visualized roentgenologically or endoscopically. In two patients the symptoms were unusual in that pain radiating to the right shoulder or to the right side of the abdomen was atypical of hiatus hernia. Dysphagia was a complaint in only one patient. Symptoms improved markedly following conservative therapy in all but one patient, who required surgical repair of the hernia.

* Received for publication July 18, 1957.

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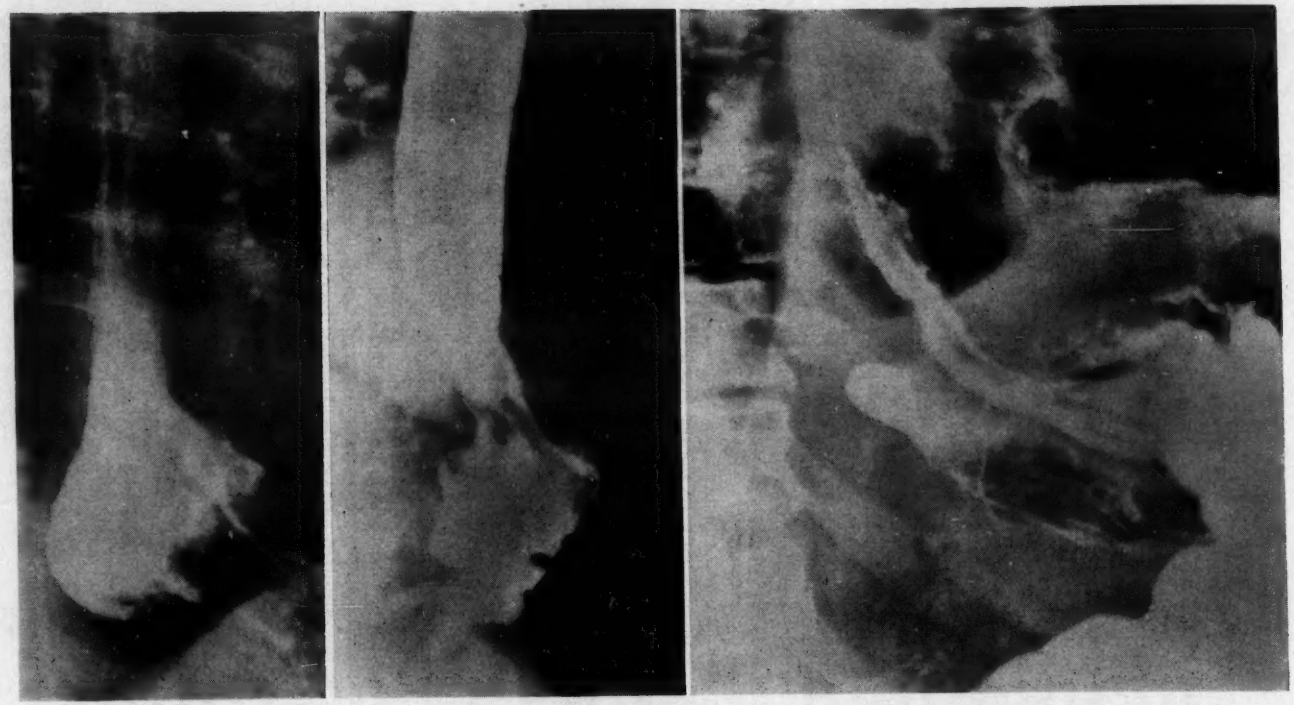
Case Reports

Case 1. A 52 yr. old male ironworker complained of heartburn and pain in the upper abdomen and chest of four years' duration. The pain was intermittent, sharp and lancinating in character, occasionally radiating to the back, and worse at night and after meals. After being awakened at night by pain he would usually sit up and fall asleep in that position. Although nausea was present frequently, his appetite was good. Vomiting used to occur only rarely and after meals, but for the last two weeks vomiting had become progressively more frequent. The vomitus contained no blood, usually just clear juice or, rarely, food. The patient was more comfortable on arising or while fasting. Nine months previously he had been operated on for a nonfunctioning calculous gall-bladder which was presumed to be the cause of his symptoms. However, his complaints persisted. He had been gassed during World War I, and he felt that his digestive difficulties had started at that time. He did not smoke, and rarely used alcohol. A bilateral inguinal herniorrhaphy as well as an anal fistulectomy had been performed 15 years previously. He had suffered a weight loss of 12 pounds during the last four months.

Physical examination revealed a moderately obese male with a blood pressure of 132/80 mm. of Hg. A right subcostal abdominal scar was present, as were scars in both inguinal regions. No viscera were palpable. There was a small, reducible umbilical hernia. The left testicle was atrophied and the right hypertrophied. Rectal examination revealed a marked stricture of the anal canal that permitted the passage of only a child's sigmoidoscope. The distal rectal mucosa appeared to be injected. A barium meal examination revealed a short esophagus. The esophagogastric junction was identified, and a hiatus hernia, 7 cm. in diameter, reducible in the erect position, was visualized (figure 1A). The rugae of the herniated stomach appeared to be thickened, but no ulceration was observed. Reflux of gastric contents was not demonstrated. Aspiration of fasting gastric juice showed 30 units of free hydrochloric acid. The remainder of the examination was within normal limits. The roentgen diagnosis was hiatus hernia (sliding). The clinical impression was reflux esophagitis due to hiatus hernia. The patient was put on the usual therapy for hiatus hernia, with postural precautions, antacids and anticholinergics when necessary. The vomiting was controlled quickly and the heartburn improved, but symptoms persisted. The patient was hospitalized for more intensive therapy, but without much success. During the next three months he lost 10 pounds, which brought his weight down to 184. Operation was advised, and repair of the hernia was attempted. Symptoms persisted postoperatively, and there was no relief from the substernal burning sensation. Despite this, the patient regained approximately 20 pounds, particularly because the ingestion of food relieved him. At this time, too, he developed nocturnal attacks of dyspnea accompanied by sour regurgitation. These attacks had been present prior to the operative intervention, but now they occurred with greater frequency. During this period his blood pressure rose to 180/100 mm. of Hg, and he was put on Rauwolfia, with an improvement in blood pressure and no apparent aggravation of his epigastric pain and distress. He was again x-rayed, and the roentgen picture was similar to the one visualized preoperatively. The hernia, however, did not reduce itself so completely in the erect position. At this time reflux could be demonstrated readily, the esophagus was not so distensible as formerly, and the contours were fuzzy and mildly serrated (figure 1B). The diagnosis was hiatus hernia with reflux esophagitis. It was quite obvious that repair of the hernia was inadequate, and further surgery was advised. At this time the repair was performed through a thoracic approach by Dr. John Garlock. Despite the technical difficulties of exploring the area following previous surgery, the sling of the posterior right crus was approximated behind the esophagus and the phreno-esophageal liga-



A B C

FIG. 1. A. The esophagus is adequately distensible. There is no radiologic evidence of inflammatory disease. The gastric pouch is well visualized. B. Following the first operation for the correction of the hernia the gastric pouch is still visualized above the diaphragm although its form has been altered. The esophageal lumen is fuzzy. C. Following the second operation the entire stomach is below the diaphragm. (The contours are distorted as a result of surgery.) The esophagus is visualized entering the cardia of the stomach in this region. The esophageal mucosa appears more sharply outlined.

ment shortened. Symptoms gradually disappeared. Six months following surgery there were no gastrointestinal symptoms. Reëxamination of the gastrointestinal tract revealed no evidence of herniation and no reflux (figure 1C).

This patient continued to have symptoms following the removal of a nonfunctioning calculous gall-bladder. Barium meal examination revealed hiatus hernia with marked reflux. An inadequate herniorrhaphy was done, without relief, and roentgen examination revealed findings similar to those visualized preoperatively. A second operation was performed via the thorax, with closure of the right crus of the diaphragm and repair of the esophagophrenic ligament. The symptoms gradually cleared, and roentgen examination two months later revealed a competent esophagogastric junction.

Case 2. This 56 year old white female presented symptoms of upper abdominal distress of three years' duration, with occasional attacks of epigastric pain, sour regurgitation and belching. The latter two complaints had become much more prominent of late, and she had resorted to bicarbonate of soda for relief. Her symptoms occurred shortly after meals or occasionally while eating. Regurgitation and heartburn with radiating pain to the neck and jaw were particularly aggravated by breakfast. Upper abdominal pain, occasionally radiating through to the back, would occur following a late meal, often waking her at night. Stooping over after a meal was particularly annoying and provoked regurgitation and heartburn. Beginning two weeks previously there had been several episodes of vomiting of bile-stained fluid. There was no hematemesis or melena at any time.

Physical examination revealed an obese female, with moderate tenderness in the right upper quadrant and epigastrium. The abdomen was otherwise negative. Rectal and sigmoidoscopic examination was normal. Gastric analysis revealed 10 units of free hydrochloric acid in the fasting specimen, and 40 units following histamine. The remainder of the laboratory examination was negative. A gastrointestinal roentgen series revealed a hiatus hernia of the sliding variety, measuring 4.5 cm. by 4 cm., reducible in the erect position (figure 2). Reflux of gastric contents was demonstrated, but no associated esophagitis could be visualized radiologically. A gall-bladder series was performed but Priodax failed to visualize the viscus. After a double dose of Telepaque there was poor visualization of the gall-bladder, but several radiopaque calculi, 0.5 to 2 cm. in diameter, were seen. The patient elected to have a cholecystectomy, which was performed without incident. Eight months later she returned with symptoms closely resembling her original complaints; these included upper abdominal distress, pain with radiation to the back, heartburn, worse at night and aggravated by food and coffee, etc. However, there seemed to be less difficulty with gas than previously. A repeat gastrointestinal examination revealed a hiatus hernia with prompt and pronounced reflux. Distensibility of the esophagus was now less apparent, and the mucosal contours were somewhat serrated and hazy. The hernia now measured at least 6 cm. in diameter. Symptoms were reproduced with the patient in the Trendelenburg position. The diagnosis was hiatus hernia with reflux and peptic esophagitis. Esophagoscopy was not performed.

The symptoms of this patient (case 2) were only slightly relieved following cholecystectomy. Heartburn and upper abdominal pain with radiation to the back and the neck were associated with findings of a moderate-sized hiatus hernia and reflux with minimal roentgen evidence of esophagitis.

FIG. 2. The hiatus hernia is well visualized and the gastric pouch presents the characteristic rugal folds. The esophagus was not visualized in this film.

Case 3. A 50 year old female was first seen because of hematemesis, melena and weakness of three days' duration. The onset was sudden, but had been preceded by several weeks of midabdominal pain radiating through to the back postprandially. Symptoms of midabdominal pain had been present prior to and following a cholecystectomy for cholelithiasis three years previously. The patient had vomited food or fluid on an average of once a month for the last three years. On occasion there appeared to be an obstruction to the passage of solid food, and rarely following the drinking of cold liquids. Her appetite had been fair, and weight loss was not prominent. The patient smoked two packs of cigarettes a day and slept poorly.

Physical examination revealed a pale, well nourished, anxious looking individual. Examination of the abdomen was noncontributory. Stools were tarry. Laboratory examination disclosed the following: hemoglobin, 9 gm.; red blood cells, 3 million; white blood cells, 4,400. The clinical impression was bleeding peptic ulcer. The patient was hospitalized, received one unit of blood, and was placed on an ulcer diet; bleeding ceased promptly. Two weeks later a barium meal examination revealed a shortened esophagus; the distal third presented a tapered appearance, with irregularity and serration of the contours. The esophagogastric junction was located 9 cm. above the diaphragm, appeared to be narrowed and fixed, and measured 4 mm. in diameter. A small projection on the right border was interpreted as the site of superficial ulceration. There was no obvious ulceration elsewhere within the herniated stomach. The hiatus hernia was 9 by 3.5 cm., and was not reduced appreciably in the erect position. The impression was stenosing esophagitis and hiatus hernia (sliding) (figure 3). Esophagoscopy revealed considerable superficial ulcera-

tion of the distal third of the esophagus, with marked narrowing. Just proximal to the esophagogastric junction there was an area of ulceration measuring 5 mm. in diameter; no active bleeding point was visualized. A tapered bougie followed by a mercury-weighted bougie was passed without too much difficulty. There was marked improvement in swallowing within 48 hours. At this time gastric analysis revealed 35 units of free hydrochloric acid in a fasting specimen. Dilatation was performed once a week for three months. This, together with the routine treatment for peptic esophagitis in association with hiatus hernia, has been followed by marked relief of symptoms.

In case 3 following a cholecystectomy for cholelithiasis, symptoms of midabdominal pain radiating through to the back and occurring postprandially persisted. After an episode of gastrointestinal bleeding, a barium meal examination revealed a hiatus hernia and peptic esophagitis with stricture. Findings were confirmed by esophagoscopy.

Case 4. A 52 year old female, the wife of a physician, was seen with a 20-year history of heartburn and epigastric pain radiating around the right side of the abdomen and through to the back. The attacks of pain usually occurred at night, often requiring narcotics for relief, and occasionally were associated with vomiting of food or liquids. Occasionally there was an achy sensation under the right shoulder blade. Heartburn, nausea and belching were common complaints. Within the last six months dysphagia had developed and the attacks had become more frequent, now accompanied by distention of the abdomen. At various times diagnoses were made of pylorospasm, postcholecystectomy syndrome, biliary dyskinesia and stenosis of the common bile duct. The patient said that as far back as she could remember she had used bicarbonate of soda for relief of abdominal distress. If this was not effective she would induce vomiting. Hot liquids or spicy foods often provoked an attack. A glass of water after a heavy meal produced severe heartburn, and food would regurgitate, "float up" into her mouth. In 1944 a gall-bladder series had revealed stones, and a cholecystectomy was performed. Shortly thereafter the symptoms recurred. She had been seen by numerous consultants, and a diagnosis of biliary dyskinesia was made. A sphincterotomy was performed, but the common bile duct was damaged during the procedure. A subhepatic abscess resulted which required evacuation. The duct was reconstructed successfully shortly thereafter, and T-tube drainage was instituted for three months. However, symptoms of upper abdominal distress persisted. Because of abdominal distention during the attacks the impression at this time was pylorospasm. An intravenous choledochogram with planigrams revealed no evidence of dilatation, obstruction or abnormality in the biliary system. A gastrointestinal x-ray series was reported as showing a "very small hiatus hernia." The impression now was that the patient was suffering from pancreatitis. She was referred for a secretin test.

Physical examination revealed a well nourished female. The abdomen disclosed right subcostal and midline suprapubic scars. There was considerable diffuse tenderness in the upper abdomen, with a more localized area of tenderness in the midepigastrium. The remainder of the examination was entirely negative. Laboratory examinations were within normal limits. Gastric analysis revealed no free hydrochloric acid in a fasting specimen, but following histamine there were 40 units of free hydrochloric acid. A secretin test revealed a volume output of 2.5 c.c. per kilogram and 160 mEq. of bicarbonate over the test period (80 minutes). The findings were consistent with normal pancreatic function. A gastric analysis performed during the secretin test revealed 72 units of free hydrochloric acid. A repeat barium

FIG. 3. The cone-shaped narrowing at the distal third of the esophagus terminates in a rigid segment 4 mm. in diameter at the esophago-gastric junction. The contour of the distal esophagus is fuzzy and serrated indicative of inflammatory disease. There is a small niche which probably represents superficial ulceration. The gastric pouch within the hiatus hernia presents no intrinsic abnormality.

A B

FIG. 4. A. The incisura probably represents the esophago-gastric junction. Some distensibility is visualized. The contour is fuzzy and serrated and represents inflammatory disease. The gastric pouch presents no intrinsic abnormality. B. Reflux of gastric contents into the esophagus is prompt and marked in the Johnstone position. The fuzziness of the contours of the distal esophagus is especially prominent in this film.

meal examination revealed a short esophagus; the esophagogastric junction was approximately 7.5 cm. above the diaphragm. A rather rigid, moderately narrowed segment marked the junction. An incisura with rigid margins was visualized on the greater curvature aspect of the esophagogastric area and suggested the presence of previous ulceration and fibrosis (figure 4A). The thoracic gastric pouch presented no apparent abnormalities. Reflux was particularly prompt and could be demonstrated at will. The patient's symptoms were reproduced during the Johnstone maneuver (figure 4B). The diagnosis was peptic esophagitis secondary to hiatus hernia with reflux. Esophagoscopy at this time was refused. The institution of therapy for hiatus hernia, with elevated position for sleeping, abstinence from food before retiring, antacids frequently during the day and before retiring, and the wearing of loose abdominal garments, has resulted in marked symptomatic improvement. The attacks of pain have subsided, and heartburn occurs only with postural provocation. However, in view of the roentgen findings and persistence of some symptoms, esophagoscopy is indicated and surgery may be necessary for permanent relief.

Case 4 underwent a cholecystectomy for cholelithiasis with no relief of symptoms. A diagnosis of biliary dyskinesia was then made and a sphincterotomy performed. During surgery the common bile duct was injured and a subhepatic abscess developed; this was drained. Later, repair of the duct was successfully performed. Symptoms persisted, and five years later a hiatus hernia, with very pronounced reflux, and peptic esophagitis were found.

Discussion

The "postcholecystectomy syndrome" has received much attention of late, and has been applied to a heterogeneous group of patients who continue to have symptoms similar to or only slightly different from their preoperative complaints. Also, it has been recognized that the group can be subdivided into particular categories, depending upon roentgen evidence of common duct stone, persistent cystic duct stump, dilated gall-bladder remnant, common bile duct stenosis, or fibrosis at the papilla of Vater, etc.[4] Another important segment that must be separated from this group includes those patients with multiple system disease, i.e., a biliary tract lesion as well as gastrointestinal disease, in whom symptoms are due to the latter disease. Cholecystectomized patients with peptic ulcer or esophagitis do not obviously belong to the group of "postcholecystectomy" syndromes, but in actual practice have been so categorized until the organic disease responsible for their symptoms was discovered. Usually, cholelithiasis has been emphasized as the important element in this combination of diseases. However, a gall-bladder with stones may be entirely silent, especially if the stones are large and/or the gall-bladder is nonfunctioning. But even if calculous disease of the gall-bladder is symptomatic, the predominant complaints may be related to the gastrointestinal system.

With increasing knowledge of the pathogenesis of peptic esophagitis and its clinical features, this condition has become a more common clinical entity. The incidence of hiatus hernia now approaches 20% in routine barium meal examination, particularly in patients over the age of 40. The presence of hiatus hernia implies, theoretically at least, that reflux of gastric contents occurs. In practice, reflux may not be demonstrable on the first examination in as many as 75% of the patients with hiatus hernia despite typical symptoms. In a high percentage of these cases barium meal examination in various positions and with recommended technics will successfully visualize this phenomenon. The employment of a cushion of foam rubber under the patient in the prone position to increase intra-abdominal pressure will exaggerate the roentgen picture of hiatus hernia and increase the reflux potential. Fluoroscopic examination in the erect position, with the patient bending forward to touch the toes (the Johnstone maneuver), will often demonstrate reflux and duplicate the characteristic symptom-complex.

More important, perhaps, a detailed history relative to postural difficulty, pain causation and radiation is often adequate to indicate the diagnosis.

It is probably true that the presence of free hydrochloric acid is a prerequisite to the development of peptic esophagitis. Peptic activity in the presence of hydrochloric acid is taken for granted because "no instance has been recorded in which pepsin is absent from gastric juice that contains HCl." [5] In the four patients in this series free hydrochloric acid was present, although only after histamine in one. While cases of esophagitis developing

following a very adequate subtotal gastrectomy in whom no free hydrochloric acid could be recovered have been reported, the factors involved may be technical rather than substantive.

Summary

Cholecystectomy for cholelithiasis was performed in four patients without relief of symptoms. In one patient, subsequent sphincterotomy for a presumptive diagnosis of biliary dyskinesia also failed to relieve the symptomatology. Gastroenterologic examination from one to eight years later revealed hiatus hernia (sliding) with peptic (reflux) esophagitis. Medical therapy produced symptomatic relief in three patients, while one required surgical intervention for repair of the hernia.

The "postcholecystectomy syndrome" is in some instances a result of inadequate preoperative investigation. Peptic esophagitis may be responsible for the symptoms of a patient with calculous disease of the gall-bladder whenever heartburn and sour regurgitation appear prominent in the clinical picture. In these patients the decision to operate for gall-bladder disease should be an indication for barium meal study. The high incidence of silent, calculous gall-bladder makes such clinical investigation mandatory to avoid some of the failures of gall-bladder surgery.

Summario in Interlingua

Le constatation de cholelithiasis o de un non-visualisabile vesica biliari non significa necessarimente que le gravamines gastrointestinal del patiente resulta ab morbo cholecystic, e similemente le symptomas que persiste post cholecystectomia non resulta necessarimente ab calculos in le ducto commun o ab le "syndrome postcholecystectomic." Esophagitis peptic pote esser responsabile pro le symptomas de patientes con morbo cholecystic quandocunque pyrosis e regurgitation acide es prominente aspectos clinic. Adequate investigationes pre-operatori, incluse un meticulose historia e un examine a repasto de barium, servi a evitar certes del non-successos in chirurgia cholecystic.

Le presente articulo include le historias clinic de quatro patientes in qui cholecystectomia a causa de cholelithiasis esseva executate sin alleviamento del symptomas. Plus tarde un plus exacte examine gastrointestinal revelava hernia de hiato con esophagitis peptic. In tres casos, alleviamento esseva effectuate per medios medical. Le quarte patiente requireva un intervention chirurgic pro le reparation del hernia.

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ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH PECTUS EXCAVATUM *

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PECTUS excavatum, or funnel chest, is said to have been first described by Bauhinus toward the end of the sixteenth Century.[1] Anatomically this deformity begins immediately below the manubrium, the sternum sloping posteriorly until its maximal concavity is reached, generally at the junction of the sternal body and the xiphoid. The center of the depression may be in the center of the chest or slightly to the right or left of the midline. As the ribs curve back to meet the depressed sternum a hollow is formed in the front of the chest, its depth depending upon the amount of sternal depression. This may be shallow or, in some instances, quite deep, the posterior sternum approaching the anterior surface of the vertebral column.

The etiology of this disorder has been ascribed in recent years to diaphragmatic muscle imbalance,[2] shortened central tendon of the diaphragm,[3] and overgrowth of the ribs.[4] Older theories, such as pressure of a body part on the sternum in utero, rickets, or the occupation of shoemaking, have largely been discarded. The role of trauma has been considered [5] but not definitely established.

Whatever the actual developmental etiology, the role of heredity is very important. Snyder and Curtis,[6] Stoddard [7] and Sainsbury [8] have reported asymptomatic families with this disorder transmitted as a mendelian autosomal dominant through three and four generations of nonconsanguineous marriages. This remarkable hereditary influence is seen in the family reported here.

Many people with funnel chest have an asthenic habitus, being tall, stoop-shouldered and slender. Patients have described symptoms such as sticking chest pain, tachycardia and breathlessness which were disabling. Some surgical groups [2, 9-15] consider these symptoms to be primarily cardiac in origin, the pulmonary system perhaps being a contributing factor. One important reason for ascribing symptoms to the cardiovascular system is the shift of the heart—usually to the left, and sometimes entirely into the left thoracic cavity—associated with this deformity. On the other hand, several other surgical groups [16, 17] have stated that the cardiac symptoms are more severe, and the circulation more embarrassed, when the sternum is depressed and the heart remains in the midline, the heart most likely being

* Received for publication June 26, 1957.
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"compressed" in this situation. For this reason they feel there is little correlation between the depth of sternal depression and the degree of symptoms. All of these groups recognize the emotional difficulties experienced by some patients with this deformity.

Several medical groups, including Edeiken and Wolferth,[18] Hutcheson,[19] Master and Stone [20] and Teplick and Drake,[21] have examined series of patients with this deformity and in most instances have found no association of the defect with symptoms, whether or not there was a shift of the heart. Those few patients with symptoms were felt to be exhibiting signs of neurasthenia, rather than organic heart disease. Evans,[22] in fact, specifically reports a group in which he feels severe cardiac cripples were produced because heart disease was unjustifiably diagnosed.

Figure 1 represents the genealogy of a family with pectus excavatum. The grandfather represents the first known generation with the deformity. His electrocardiogram was within normal limits, though he was past 80 at the time it was taken. All four of his children have a marked sternal depression. Their electrocardiograms were within normal limits. In the third generation there were eight grandchildren, only five of whom were available for examination. These all had funnel chest deformities. Electrocardiograms were taken on four, of which two were normal and two were unusual and will be presented. In the fourth generation there is one great-grandchild with a definite but as yet slight deformity. In this entire group there are no symptoms or any unusual emotional reaction referable to the deformity.

Of 13 possibilities, there are 10 definite inherited cases of pectus excavatum. Since a dominant trait assumes at least 50% transmission, and

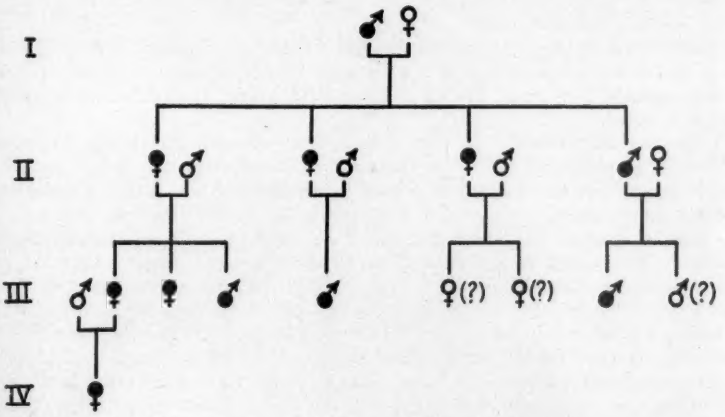

FIG. 1. Genealogy of a family with pectus excavatum, with transmission through four generations of nonconsanguineous marriages. Black circles indicate patients with sternal depression.

is strongly suggested by lineal descent through three generations of nonconsanguineous marriages,[8] it would appear in this study, as in others, that the trait is dominant.

In addition to the two patients noted above, four other cases with funnel chest deformities and interesting electrocardiograms will be presented.

Case Reports

Case 1. This 26 year old white male was first examined June 19, 1954, shortly after his discharge from the Army. The patient was asymptomatic and led an extremely active, energetic life. Except for a well marked, deep and wide funnel chest deformity, physical examination was negative. Blood pressure and routine laboratory examinations were normal.

X-rays of the chest (figure 2) revealed the deformity, particularly on the lateral view. The heart was essentially in the midline, with little or no displacement. The hilar markings appeared to be exaggerated.

Electrocardiographic examination (figure 3) showed T_1 to be flat, T_2 low, a small, short Q in aVL with T inverted, T deeply inverted in V_2 through V_5, and T flat in V_6. The pattern was improved slightly by exercise. The response to a Valsalva maneuver [29] was normal.

During the last three years the patient has continued to be active and asymptomatic. Electrocardiograms during this time have shown occasional waxing and waning in the depths of the T waves in the leads noted, the pattern remaining essentially the same.

Case 2. A 31 year old white female, a sister of the previous patient, was first examined on August 17, 1954. She has had Raynaud's disease for a number of years but was otherwise asymptomatic. Physical examination revealed evidence of peripheral vascular disease and a well developed funnel chest deformity, but was otherwise negative. Blood pressure and routine laboratory procedures were normal. Her response to a Valsalva maneuver was normal.[29]

A chest x-ray (figure 4) showed a shift of the heart to the left in the posteroanterior view, with exaggeration of the hilar markings. On the lateral view the sternal depression was well seen.

An electrocardiogram (figure 5) showed a small QRS in Lead 1, deep Q_2 and Q_3 with T inverted in Lead 3, deep Q in aVF with T upright, and deep Q in V_4 through V_6, with upright T waves. The Q is about 0.02 second in duration in the leads in which it is noted.

Follow-up examinations of this patient have revealed no change in x-ray or electrocardiographic findings. Her Raynaud's disease remains static, and she is asymptomatic. She has at present a four year old child who has a definite but as yet slight funnel chest.

Cases 3 through 6. These patients have mild to moderate funnel chest deformities. They range in age from 22 to 37 years of age. Their hearts are in the midline, except for case 3, in whom there is a slight shift of the heart to the left. Cases 3 and 4 (figure 6) have tall R′ in the right-sided chest leads, with the QRS measuring 0.12 second in case 3 and 0.14 second in case 4. In case 4 the R′ is best seen in V_1 2H (two interspaces higher than V_1).

In cases 5 and 6 (figure 7) there is an R′ in the right-sided chest leads, mainly V_4R. The QRS measures 0.10 second in duration. There is notching of the R waves in Leads 2, 3 and aVF. Though these last two tracings might be considered variants of normal, they fulfill many of the criteria for incomplete right bundle branch system block.

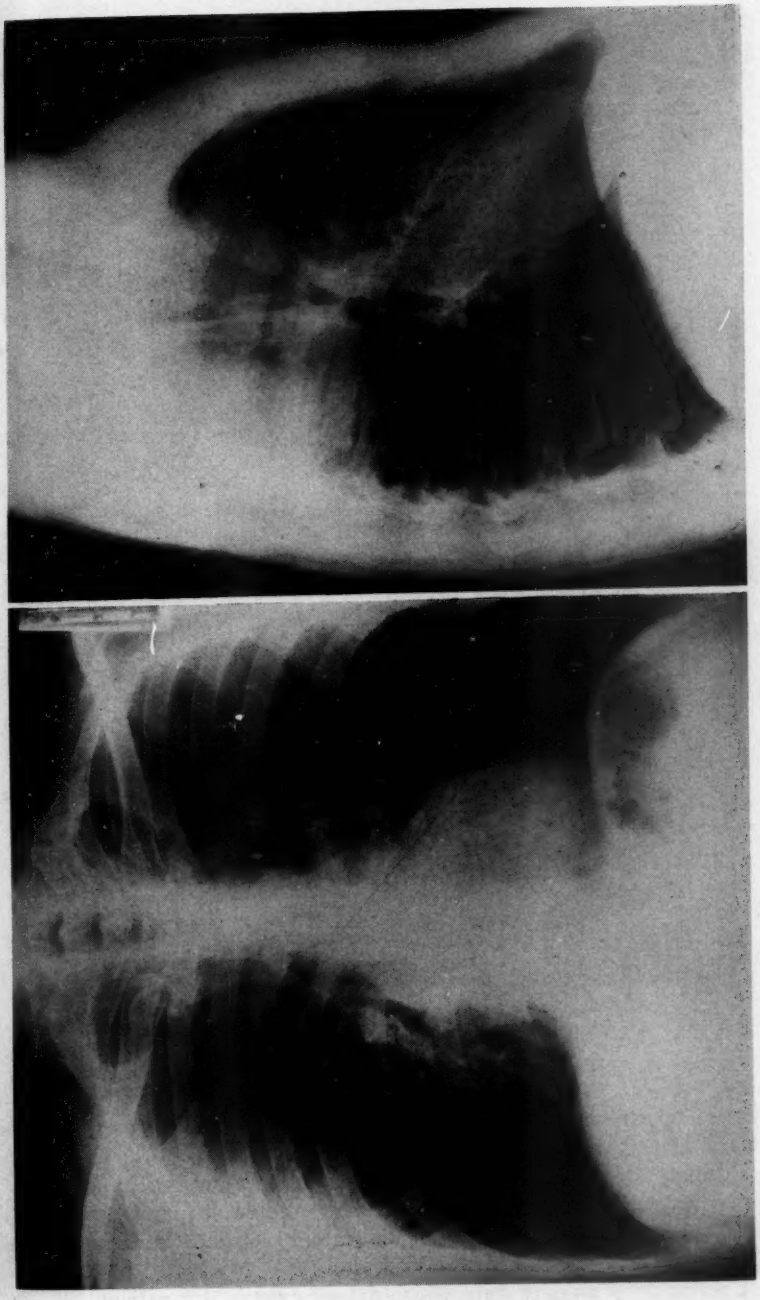

FIG. 2. Posteroanterior and lateral chest x-ray of case 1.

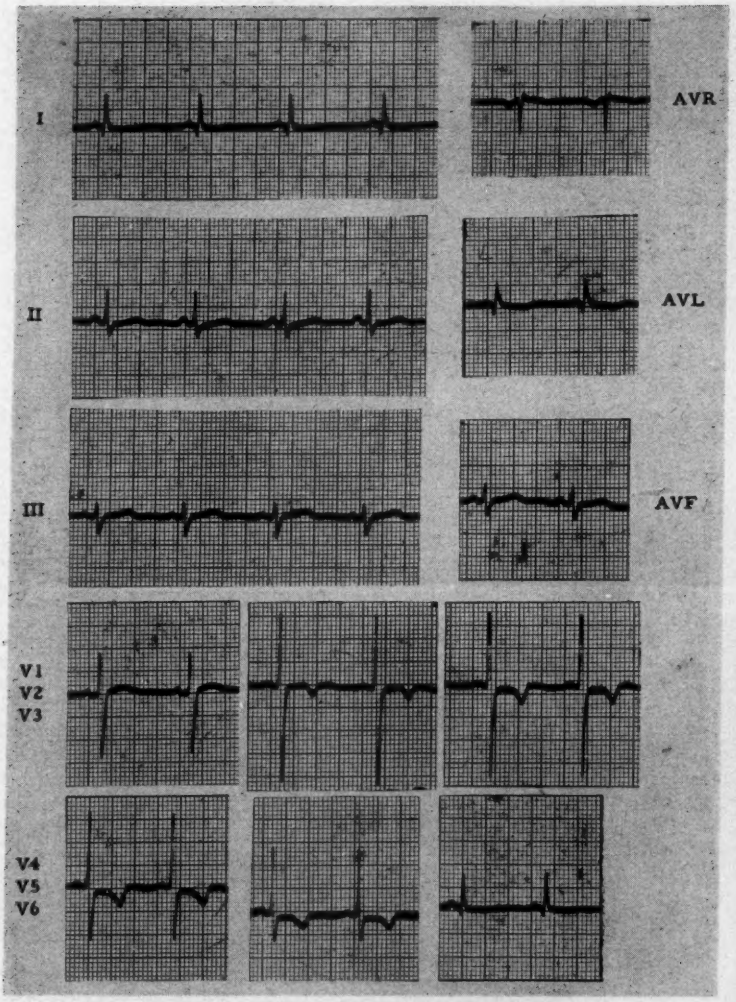

FIG. 3. Electrocardiogram of case 1.

DISCUSSION

Case 1 electrocardiographically suggests, among other things, anterior coronary artery disease. Myocarditis, pericarditis, beriberi, myxedema, hypokalemia, and the persistent "juvenile pattern" described by Littman [23] may produce similar findings. Most of these can be ruled out by the clinical well being of the patient. The "juvenile pattern" is almost invariably found in the Negro, and as studied by Wasserburger [24] appears to be associated with a severe overt anxiety state, which did not exist in this patient.

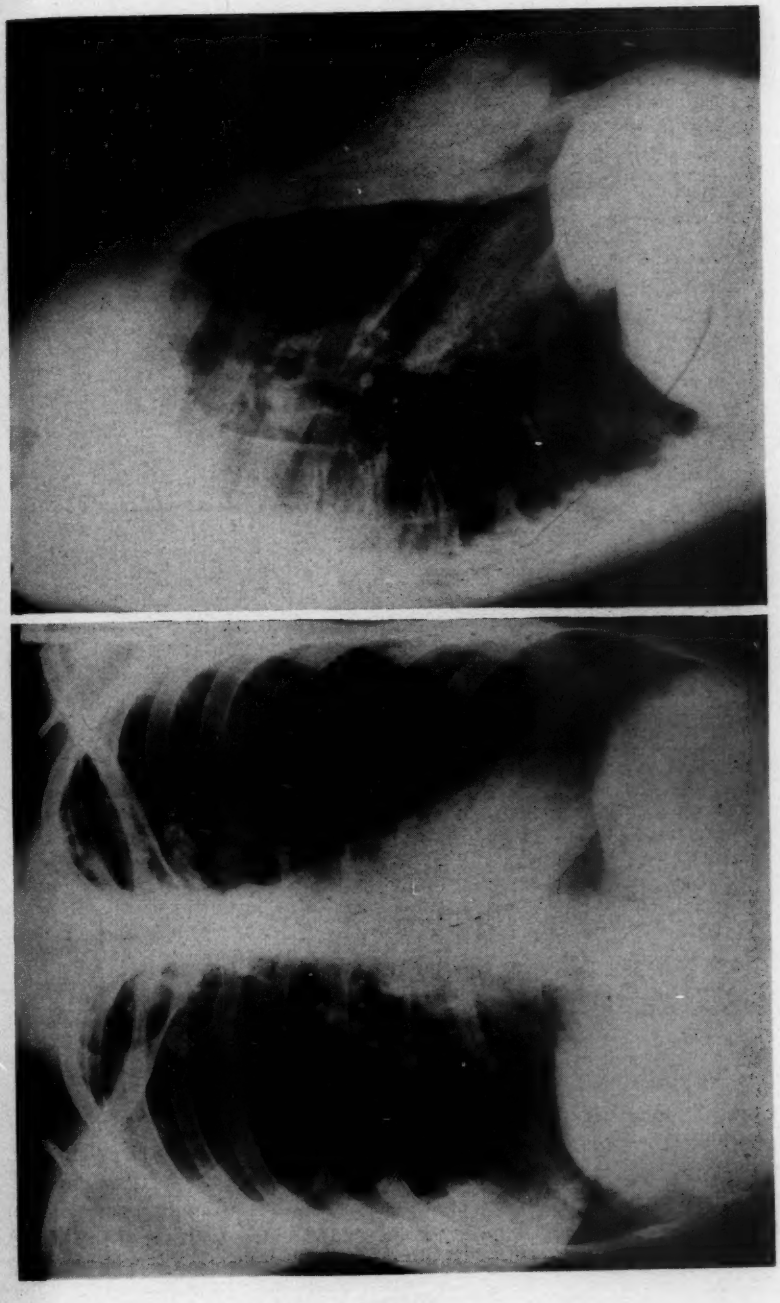

FIG. 4. Posteroanterior and lateral chest x-ray of case 2.

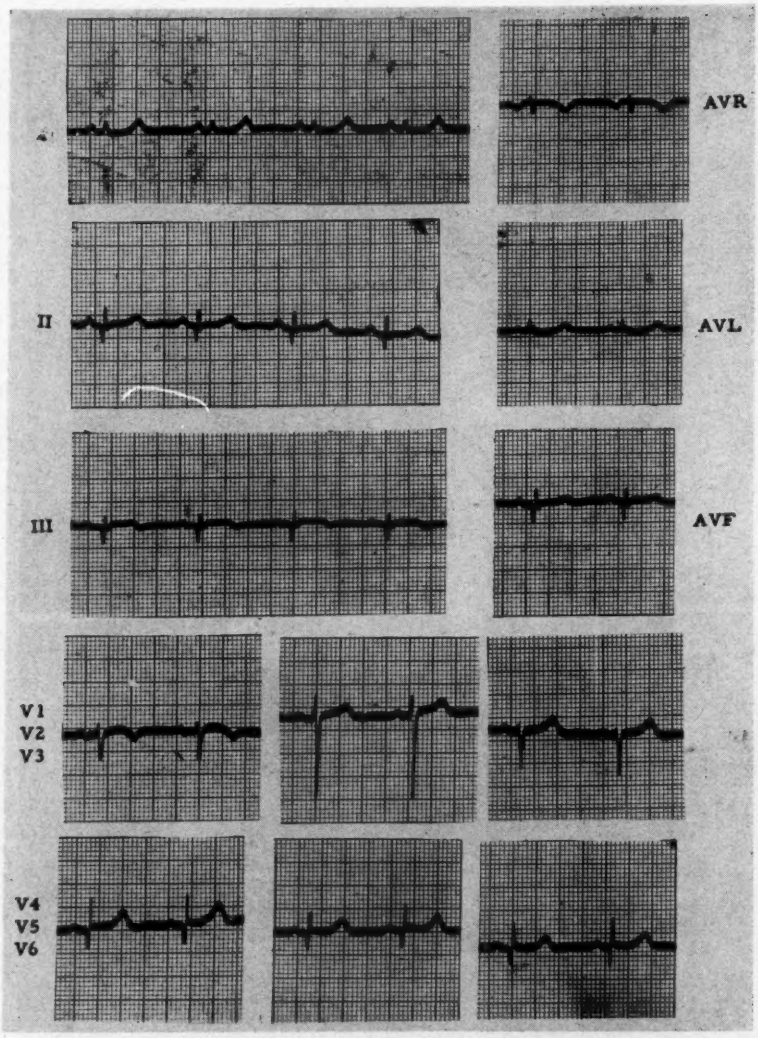

FIG. 5. Electrocardiogram of case 2.

Clinically the patient is in excellent health; there is no venous congestion, and nothing to suggest interference with diastolic filling. Dressler and Roesler [25] have reported a similar pattern in funnel chest deformity, but the T wave changes were not so extensive as those noted in this patient. These electrocardiographic changes appear to be related to the position of the heart, lying in the midline immediately behind the sternal depression. The changes

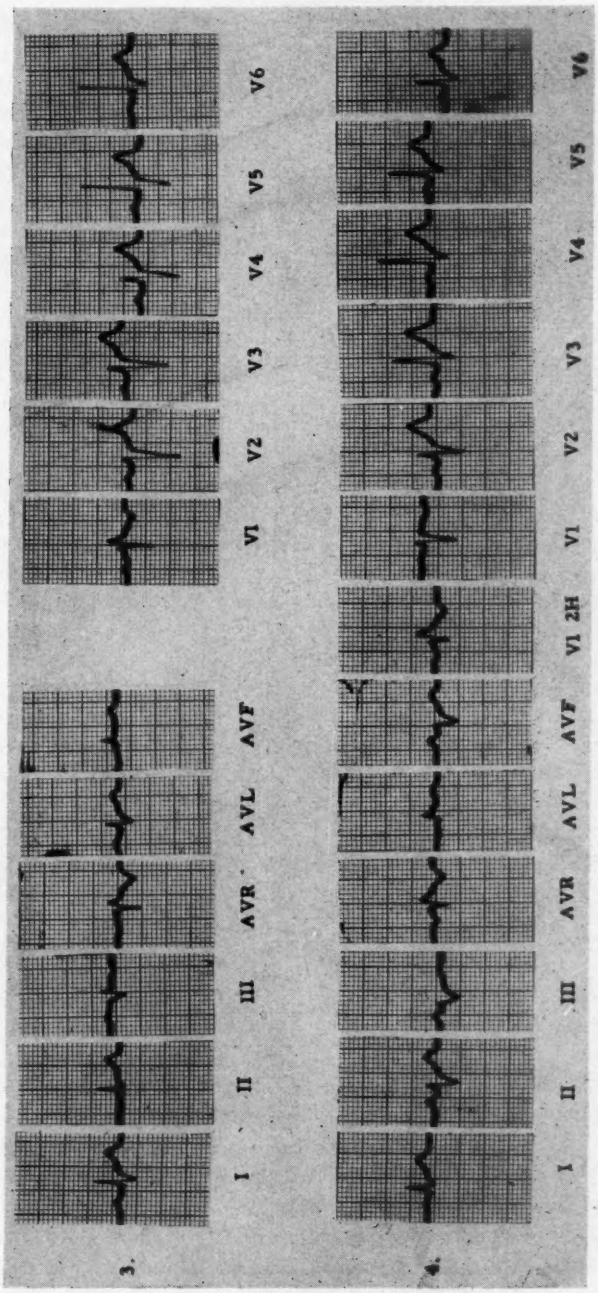

FIG. 6. Electrocardiograms of cases 3 and 4, with pattern suggesting complete right bundle branch block.

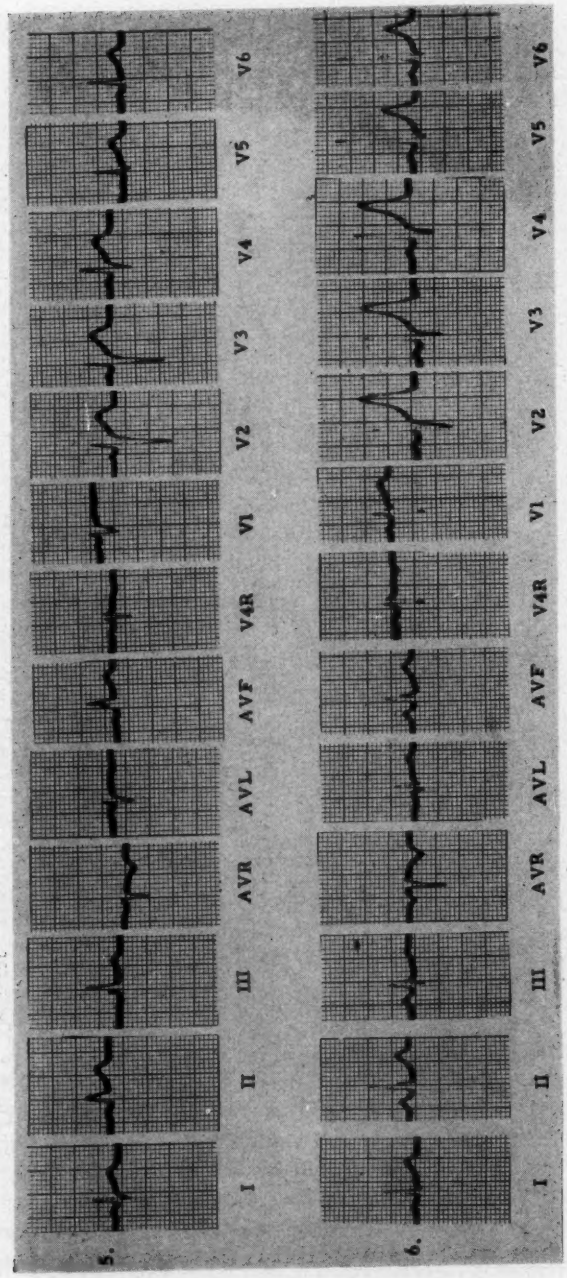

FIG. 7. Electrocardiograms of cases 5 and 6, with pattern suggesting incomplete right bundle branch block.

of repolarization noted may be the result of pressure of the depressed sternum on the anterior cardiac surface.

It is quite interesting to note that the patient is asymptomatic, which is not in keeping with statements previously cited that this type of patient is particularly likely to have symptoms due to cardiac compression.

In the second patient there is no clinical evidence of coronary artery disease, despite a tracing suggesting posterolateral wall infarction. The lack of any abnormality of repolarization and the shortness of the Q waves, together with the excellent physical condition of the patient, suggest the electrocardiographic findings may be the result of an anatomic shift of the heart, due to the chest deformity as seen on x-ray. As a result of this shift the initial septal forces are directed entirely away from the posterolateral electrode positions and give rise to the deep but short initial downward deflections.

The patient's peripheral vascular disease appears to be an unrelated entity.

Two patients had prolonged conduction times, with an R′ in the right-sided precordial leads. Two patients had conduction times at the upper limits of normal, with R′ in right-sided chest leads and notching of the QRS complexes. Patients with R′ in right-sided chest leads have been reported by Botelho and Mederiros,[26] Schaub and Wegmann,[27] and Wachtel, Ravitch and Grishman.[28] The latter group feels from vector analysis that the pattern is due to cardiac position, V_1 registering terminal cardiac depolarization directed toward this lead as a result of position, rather than as a result of any conduction disturbance. In the two patients reported above, and several of those of Schaub [27] with prolonged conduction times and the pattern of right bundle branch system block, a true disturbance of conduction would appear to be likely. These patients have all been asymptomatic. The fortuitous finding of an unassociated benign form of right bundle branch block is possible but not likely, considering its not infrequent occurrence in this disorder.

Nonspecific electrocardiographic changes in patients with pectus excavatum have been reported by authors using three or four leads, which are not directly comparable to our cases. Paroxysmal tachycardias [4, 15, 18, 21, 26, 27] have also been reported.

In this report we have presented six patients with funnel chest deformity with electrocardiographic changes suggesting anterior and posterior coronary artery disease and complete and incomplete right bundle branch block. It is our feeling that all these changes are a result of the chest deformity, as a result either of pressure or of cardiac position.

The patients presented are asymptomatic and well adjusted, having no cardiorespiratory symptoms or anxiety that can be attributed to their chest deformity. Nevertheless, some patients with this deformity display physical and emotional symptoms which have been attributed to their deformity and

which have been the basis for surgical repair. It is not the purpose of this paper to review the indications for such surgical intervention, other than to state, on the basis of our experience and a review of the literature, that there is no well defined, consistent physiologic abnormality associated with this deformity. We should like to point out that electrocardiographic changes may occur, that they may resemble those associated with coronary artery disease or right bundle branch block, and that they in themselves should not be considered, at least in our experience, an indication of organic heart disease.

Summary

Six patients are presented with pectus excavatum and electrocardiograms resembling anterior and posterior coronary artery disease, and complete and incomplete right bundle branch system block. These changes are thought to be related to the anatomic position of the heart, or pressure of the sternal deformity on the anterior cardiac surface. The patients are asymptomatic and have been followed for some years without any evidence of organic heart disease.

Summario in Interlingua

Es presentate un familia in qui le deformitate de pectore excavate esseva presente como dominante autosomal mendelian in quatro generationes.

Esseva studiate le alterationes electrocardiographic presente in sex patientes con pectore excavate. Iste alterationes es simile a illos de morbo de arteria coronari anterior e posterior e a illos de complete e incomplete bloco de branca dextere. Signos clinic de morbo cardiac non esseva presente in ulle del patientes. Omnes se trovava in bon stato de sanitate, e omnes esseva ben adjustate (in despecto del facto que anxietate occurre con alte grados de frequentia in patientes con iste deformitate).

Es opinate que le observate alterationes electrocardiographic resulta del pression del sterno super le fronte del corde o del displaciamento del corde in le thorace in consequentia del deformitate de pectore excavate. Esseva notate nulle signo a indicar que le replenation diastolic esseva impedite.

Es concludite que anormal alterationes electrocardiographic in patientes con pectore excavate non debe esser considerate per se como indication del presentia de organic morbo cardiac.

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COMPLICATIONS OF LONG-TERM DIABETES MELLITUS*

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Reports in the literature indicate that as our diabetic population ages the frequency of premature vascular complications increases. Some observers [1, 2, 3] are of the opinion that these degenerative changes are inevitable, provided the diabetic lives long enough. Dolger [4] has suggested that the accelerated vascular lesions are an associated phenomenon and not a complication of diabetes. Others have emphasized the control of diabetes, duration of the disease and age of onset as causative factors in the development of vascular complications. On the basis of their extensive experience, Joslin and his colleagues [5, 6, 7] are convinced that premature diabetic arteriosclerosis can be avoided.

Present Study

This report consists of an analysis of 137 cases of diabetes mellitus. Eighty-four patients of this series attended the Metabolic Clinic of the Research and Educational Hospitals. Henceforth, this group will be designated as "clinic cases." The remainder of the series (53 cases) have been under the care of one of us (J. T. P.) as private patients. We shall refer to this group as "office cases." Diabetes has existed for 15 or more years in all cases studied.

The office series includes 27 females and 26 males. Ages range from 22 to 84 years. At the time of examination, 31% were 22 to 35 years of age, 28% were 36 to 55 years, and 41% were over 55 years. Females predominated in the group of clinic cases. Of the 84 cases studied, 58 were female and 26 were male. They varied in age from 15 to 79 years. The majority of these (70%) were over 55 years of age. There were only 12% in the 15- to 35-year age group, and 18% in the 36- to 55-year age group.

Table 1 shows the duration of diabetes. Thirty-three of the office patients had had diabetes for from 15 to 24 years, and 20 had been diabetic for 25 or more years. Most of the clinic patients (74) had been known to have diabetes for from 15 to 24 years. In only 10 cases had the duration of the disease exceeded 25 years. The age at onset of diabetes is noted in

* Received for publication June 25, 1957.
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TABLE 1

Duration of Diabetes

Years	Number	
	Clinic Cases	Office Cases
15–19	47	21
20–24	27	12
25–29	8	16
30 or more	2	4
Total	84	53

table 2. Seventeen of the office patients and 12 of the clinic patients can be classified as juvenile diabetics, since the disease had developed during the first 15 years of life. At the time of onset, seven office patients and 22 clinic patients had been more than 50 years of age.

The dosage of insulin used is shown in table 3. With the exception of one office case and nine clinic cases, all patients required insulin for management. Severity of the diabetic state as judged by the insulin requirements seemed to be greater in the office cases. (In this group, 29 patients (55%) used more than 50 units daily.) It should be noted, however, that there were many more elderly diabetics among the clinic patients. At the present time, most of the patients take NPH insulin or combinations of NPH and

TABLE 2

Age at Onset of Diabetes

Years	Number	
	Clinic Cases	Office Cases
15 or less	12	17
16–29	6	15
30–49	44	14
50 or more	22	7

protamine-zinc insulin. It is to be understood that in many instances multiple injections of regular insulin were used in the early years of the disease. With the introduction of protamine-zinc insulin, mixtures of regular and depot insulin or separate injections of each were taken.

Thirty-two patients (60%) of the office group have been observed and under management for 11 or more years. Most of these patients were examined in the office three or four times annually. The clinic patients were followed for periods varying from one to 22 years. Twenty-seven of the total of 84 were under observation for over 11 years. Clinic visits were usually at one- to three-month intervals.

TABLE 3

Dosage of Insulin

Insulin	Clinic Cases	Office Cases
None	9	1
Up to 30 units	25	11
31 to 50 units	37	12
Over 50 units	13	29

The degree of control of the diabetic state was estimated on the basis of the following criteria:

Good Control:

1. Insulin administration instituted within a few weeks of onset of diabetes.
2. Strict adherence to diet, with careful measurement of food.
3. Maintenance of weight.
4. Frequent urine examinations.
5. Regular physical examinations, including blood sugar determinations, at least once annually.

Fair Control:

1. Insulin administration instituted within two years after onset of diabetes.
2. Diet not constantly weighed or measured with occasional laxity in adherence to diet.
3. Maintenance of weight.
4. Urine examinations for sugar one or more times weekly.
5. Irregular physical examinations and blood sugar tests.

Poor Control:

1. Frequent episodes of acidosis, and coma more than once.
2. Insulin taken irregularly.
3. Marked laxity in adherence to diet.
4. Infrequent urine examinations for sugar.
5. Rare physical examinations and, when done, fasting blood sugar values usually over 200 mg. per 100 c.c.

According to these standards, only 9.5% of the 84 clinic patients could be considered as being under good control. A larger group of good control cases (26.4%) was encountered in the office series (table 4).

Tables 5 and 6 illustrate the incidence of degenerative complications in relation to the duration of the disease, the age of onset and the degree of control. The data presented have been adjusted to give proportional distribution of cases with onset over or under 15 years of age and duration of diabetes over or under 20 years within the three major diabetic control groups. The probability of the observed distribution's occurring by chance alone was found to be less than one in 1,000 (e.g., P 0.001) for the number

TABLE 4

Degree of Control

Control	Clinic Cases		Office Cases	
	No.	%	No.	%
Good	8	9.5	14	26.4
Fair	44	52.4	24	45.3
Poor	32	38.1	15	28.3

TABLE 5

Incidence of Complications

Groups					Percentage Showing Complications			Percentage Showing None of These Complications
Degree of Control	No. of Cases	Age at Onset Mean ± S. D.	Duration of Diabetes Mean ± S. D.	Daily Insulin Mean ± S. D.	Retinopathy	Hypertension	Albuminuria	
Good	22	34 ± 17	22 ± 5	37 ± 20	14	32	9	59
Fair	68	34 ± 17	20 ± 6	39 ± 25	44	32	31	31
Poor	47	35 ± 15	20 ± 4	41 ± 26	72	57	47	9

of cases showing retinopathy in both the unadjusted and the adjusted data. P value was less than 0.02 for hypertension and less than 0.01 for albuminuria in both the unadjusted and the adjusted data. The mean and standard deviation of the age of onset of diabetes, duration of diabetes and daily insulin requirements were determined for the "degree of control" groups. No significant differences were noted.

Patients who fulfilled the criteria of good control showed a much smaller incidence of complications than did those classified in the fair-control and poor-control groups. Hypertension existed to an equal degree in both the good-control and the fair-control groups. Freedom from complications decreased markedly as the degree of control lessened. Thirteen of the 22 good-control patients had no retinopathy, hypertension or albuminuria.

TABLE 6

Incidence of Complications in Relation to Degree of Control, Duration and Age at Onset of Diabetes Mellitus

Degree of Control and Number of Cases	Duration.....	Number of Cases			
		15–19 Years		20+ Years	
	Complications \ Age at Onset	0–15 Years	16+ Years	0–15 Years	16+ Years
Good 22	Retinopathy	1	1	—	1
	Hypertension	—	4	—	3
	Albuminuria	—	—	—	2
	None of above	1	4	2	6
Fair 68	Retinopathy	1	14	2	13
	Hypertension	—	9	—	13
	Albuminuria	3	9	2	7
	None of above	2	8	5	6
Poor 47	Retinopathy	5	13	4	12
	Hypertension	3	13	1	10
	Albuminuria	4	7	3	8
	None of above	—	2	1	1

Only four of the 47 poor-control cases did not demonstrate these complications (table 6).

Cases were divided into the following four categories: (1) age at onset, 15 years or less, and duration of diabetes, 15 to 19 years; (2) age at onset, 15 years or less, and duration, 20 or more years; (3) onset, over 15 years of age, and duration, 15 to 19 years; and (4) onset, over 15 years of age, and duration, 20 or more years.

The age of onset of diabetes appears to be a factor in the development of degenerative complications. There were fewer cases free of complications in the good-control group among those with onset of diabetes under age 15 than among those with onset after 15. Similar findings were observed in the fair- and poor-control groups. An attempt was made to evaluate the duration of the diabetic state as a contributing factor to the incidence of vascular complications. There was not a greater incidence of complications in the group of cases with duration of 20 or more years than in the group of 15 to 19 years' duration.

Discussion

The frequency of occurrence of vascular disease associated with diabetes mellitus is generally recognized. The pathogenesis, however, is not clearly understood. The reported incidence of vascular complications varies, depending upon the age of onset and the duration of the disease. Considerable controversy exists as to the importance of control of the diabetic state.

Of the 137 cases comprising this report, 29 (21%) had developed diabetes at age 15 years or less, and can be classified as juvenile diabetics. In this group of 29 patients, retinopathy was present in 13, hypertension in five, and albuminuria in 13. The findings obtained are compared with those of other reported series in table 7.

Larsson, Lichtenstein and Ploman [11] report that, after more than 15 years' duration, 72% of a series of 33 juvenile diabetics had some form of retinopathy, and 30% showed albuminuria. All patients were permitted a "free diet" with controlled insulin treatment. On the basis of their findings and comparisons with diet-treated series, Larsson concluded that the use

Table 7

Reported Incidence of Complications in Juvenile Diabetes of 15 or More Years' Duration

	(8) Chute (1948)	(9) Jackson (1950)	(10) Daeschner (1951)	(11) Larsson (1952)	(12) Lundbaek (1953)	(13) Forsyth (1956)	This Study
Number of Cases	27	34	25	33	24	41	29
Retinopathy	59%	68%	80%	73%	83%	59%	45%
Albuminuria	29%	6%	32%	30%	25%	20%	45%
Hypertension	19%	6%	36%	34%	33%	7%	17%

of measured diets does not protect the patients against degenerative vascular complications to a greater extent than does treatment with a free or normal diet. The only other group of diabetics allowed "free diets" included in table 7 is that of Forsyth and Payne.[13]

On comparison with other series it would seem that the incidence of albuminuria was high (45%) in our group of 29 juvenile diabetics. This may have resulted from the inclusion of cases showing as little as a trace of albumin intermittently. Patients with duration of diabetes of 15 to 19 years revealed the presence of retinal lesions more often than did patients whose disease had lasted longer than 20 years. Most reports, however, indicate a proportionate increase in the incidence of retinopathy with increasing duration of diabetes.

Recently White [14] reviewed the course and prognosis of 879 juvenile diabetics surviving more than 20 years. Examination revealed that retinopathy occurred in 82%, hypertension in 32% and albuminuria in 41%. At 35 years' duration, nearly all showed lesions; 93% had retinopathy, 53% had hypertension and 44% had nephropathy. Although such statistics are discouraging because of the high incidence of vascular lesions, a truly morbid pattern has been presented by Fanconi.[15] He reported 100% mortality from nephropathy in juvenile diabetes after a 20-year duration of the disease.

In our series of 137 cases of diabetes mellitus, 38 (28%) were found to be free of retinopathy, elevated blood pressure levels and albuminuria. The duration of diabetes was 15 or more years in all cases, and was in excess of 25 years in 30 patients. Dolger [4] reported that the earliest retinal lesions were noted about 13 years after the onset of diabetes, and were associated with hypertension or albuminuria in about 50% of the 200 patients observed. Regardless of age of onset or treatment used, all patients revealed retinopathy within a period of 25 years' duration of diabetes.[2] This depressing statement is opposed by a number of reports [16, 17, 18, 19, 20] in the literature, in addition to the findings of the present small group of cases. Tables 5 and 6 indicate the relationship of the incidence of complications to control of the diabetic state. It is to be noted that the incidence of retinopathy is minimal in the patients under good control. Examination of the total series revealed a greater incidence of vascular complications among the clinic cases. These findings are graphically illustrated in figure 1. Analysis of the data presented shows that the clinic cases differ from the office cases in several aspects. Seventy per cent of the clinic patients were over 55 years of age, as contrasted to 41% in the office group. This in itself would tend to predispose them to degenerative vascular complications. There is a distinct difference in the age of onset of the diabetes in the two groups. Diabetes was first diagnosed before the age of 30 years in the majority of the office patients, whereas the age of onset was greater than 30 years in 66 of the 84 clinic patients. Insulin requirements were higher in the office

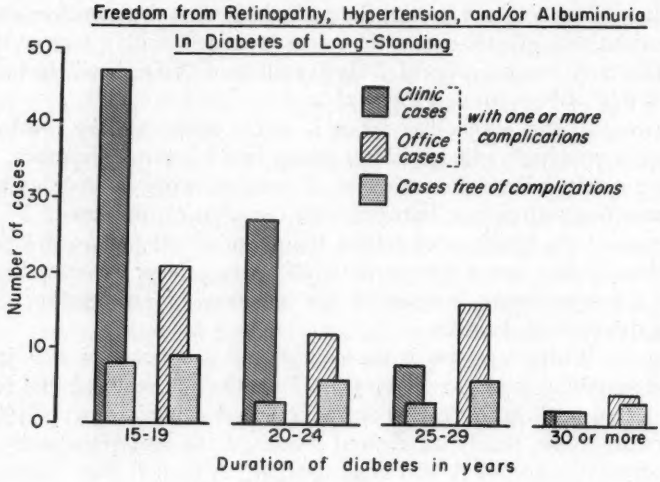

FIG. 1.

patients, and this was no doubt due to the earlier age of onset of diabetes among this group. There is a much larger percentage of patients classified as "good-control" cases in the office group than in the clinic group (table 4).

Such a marked difference in the degree of control may be due in part to (1) superior economic standards in the private patient group, (2) closer contact between the physician and private patients, (3) greater continuity of management, and (4) higher levels of intelligence and coöperation among the office patients.

From the present study it appears that the degree of diabetic control plays a major role in the development of degenerative vascular complications. The age of onset and the duration of diabetes are undoubtedly contributing factors. It is significant that 59% of the patients under good control were free of retinopathy, hypertension or albuminuria, in contrast to only 9% among the poor-control group.

SUMMARY

1. A study of vascular complications in a series of 137 cases of long-term diabetes mellitus is presented. In 30 cases the duration of diabetes exceeded 25 years. A comparison of clinic patients and private patients is made.

2. Approximately 50% of the 29 juvenile diabetics showed absence of retinopathy.

3. Thirty-eight cases of the total series were found to be free of retinopathy, hypertension and albuminuria.

4. The degree of control appears to be a significant factor in the development of vascular complications in long-term diabetes mellitus.

Acknowledgment

We are indebted to Dr. William R. Best, of the Department of Medicine, for the statistical analysis of the data.

Summario in Interlingua

Iste reporto presenta un studio del complicationes degeneratori constatate in 137 casos de diabete mellite. In omne iste casos, diabete habeva existite durante 15 annos o plus. In 30 casos le duration del morbo excedeva 25 annos. In 29, le disveloppamento de diabete habeva occurrite ante le etate de 15 annos. Le serie consiste de patientes private e de alteres vidite in un clinica pro patientes visitante. Le stato del control del diabete esseva classificate como bon, satis bon, e non bon, de accordo con un gruppo de criterios listate. Vinti-duo patientes satisfaceva le criterios de un bon grado de control. In 47, le grado de control esseva considerate como non bon. Es presentate datos pro illustrar le incidentia de complicationes degeneratori in relation al duration del morbo, al etate del patiente quando le morbo se declarava, e al grado de control effectuate. Patientes in qui le control esseva bon monstrava un multo plus basse incidentia de complicationes que patientes in le duo gruppos in le quales le control esseva classificate como satis bon e non bon. Dece-tres del 22 patientes a bon grados de control habeva ni retinopathia ni hypertension ni albuminuria. Iste complicationes esseva absente in solmente quatro del patientes a non bon grados de control. Un plus alte incidentia de complicationes vascular esseva notate inter le patientes vidite al clinica que inter illes del practica private.

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THE CLINICAL EVALUATION OF SUSTAINED RELEASE ANTITUSSIVES *

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Introduction

In recent years significant advances have been made in the development of forms of medication which will more effectively provide the patient with the total daily prescribed dose. These newer forms of medication eliminate the necessity of taking doses of medicine at two-, three- or four-hour intervals. The common goal in the development of sustained release preparations is to provide a medication that will be clinically effective with a maximum of one or two oral doses in a 24-hour period. A sustained release preparation is one that will yield predictable amounts of the active component over an extended period of time. To evaluate the effectiveness of the amount of drug released, and to assess its clinical value, reliable methods for obtaining these data in clinical investigations are needed.

Gelvin and his co-workers [1] approached this problem by studying the continuance of coalescence of barium sulfate granules utilizing the common technic of various diameters and thicknesses of enteric coatings. The rate of disintegration of these coated granules was studied in men by following their course through the gastrointestinal tract by x-ray. Since barium sulfate is virtually insoluble in the gastrointestinal juices, it is questionable whether this technic could be applied to substances that are highly water-soluble. One obvious difficulty is the problem of leaching from granules which have an imperfection in their coating.

Reports of blood level studies supporting the slow release of orally administered drugs are very limited. Radio tracer technics would be exceedingly reliable, but obviously are limited in scope when applied to human studies. The substitution of animals for humans will provide some information but cannot be completely comparable because of the uniqueness of man's gastrointestinal tract. Therefore, carefully controlled and statistically valid clinical studies of the therapeutic effectiveness of a sustained-acting drug are undoubtedly the best approach to the problem. Such an approach is herein reported, using cough suppression as an example.

One of the most satisfactory means of developing a sustained-release medication is to prepare a chemical complex of the drug with an ion-ex-

* Received for publication August 16, 1957.
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change resin. In the gastrointestinal tract, the drug is released from the resin complex as a result of ion exchange, thus making it available for its intended physiologic action. If the resin drug complex has the proper composition, a slow, predictable rate of liberation of the active drug in the gastrointestinal tract may be expected. In the example cited here, a new drug was used which consisted of an ion-exchange-resin complex with dihydrocodeinone, a highly active antitussive drug. It had been previously shown [2] that such a complex was highly effective in suppressing induced cough in animals. Consequently, this study was undertaken to evaluate clinically the prolonged antitussive effect of the drug.

Design of the Clinical Investigation

To secure statistically valid results, it was necessary to observe the cough-suppressing effect of the drug in patients for a period of 12 hours after the administration of a single dose. The double-blind technic, as described by the authors,[3-5] was again the method of choice for this study. A clinical comparison between a placebo and the dihydrocodeinone resin complex at two dose levels was undertaken. All three preparations were made into identical looking tablets and were coded Q, R and T by the supplier.* The code was not revealed to the investigators until the statistical analysis had been completed.

Each of the three preparations, Q, R and T, was given to 77 patients for a period of seven days. The sequence was randomized to minimize overlapping effects of previously given medications.

Personal observations on all patients were made, beginning at 7 a.m., 10 a.m., 1 p.m., 4 p.m. and 7 p.m., respectively, by a nurse specifically assigned to this duty during the three weeks of this study. Thus, for the

Name Age Cough: Acute ☐ Dry ☐ R.F.
No. Male ☐ Chronic ☐ Prod. ☐ Starting
Diagnosis Female ☐ Noc. ☐ Date:

D	Hr.	3 Hr.	6 Hr.	9 Hr.	12 Hr.	Tot.	Adm.	3 Hr.	12 Hr.	Tot.	Remarks
1		Relief	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4			0 1 2 3 4	0 1 2 3 4		
2		Relief	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4			0 1 2 3 4	0 1 2 3 4		
3		Relief	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4			0 1 2 3 4	0 1 2 3 4		
4		Relief	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4			0 1 2 3 4	0 1 2 3 4		
5		Relief	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4			0 1 2 3 4	0 1 2 3 4		
6		Relief	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4			0 1 2 3 4	0 1 2 3 4		
7		Relief	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4			0 1 2 3 4	0 1 2 3 4		
Tot.											

Fig. 1. Patient record card.

* The dihydrocodeinone resin complex is incorporated into "Tussionex," produced by the R. J. Strasenburgh Co.

duration of the study, observations were made on all patients by the same individual. It was found that one person was able to visit each of the patients within the three-hour time interval. Larger groups would require additional personnel and would therefore complicate the analysis by the introduction of additional unknown factors. Medication under code name was given at 7 a.m. and at 7 p.m. throughout the trial. The amount of cough relief was recorded on special cards (figure 1) and expressed as a numerical value (0 = no relief; 4 = maximal relief). Side-effects, if any, were also noted.

Discussion of Results

Sixty-seven of the 77 patients included in this study were observed each day as scheduled for the entire three-week period. This means that a total of 7,035 individual observations was made in the first study. The group of patients consisted of persons with chronic cough as a result of tuberculosis, chronic respiratory infection, etc. Because of the special design of the individual patient observation cards, the daily and hourly totals could be easily compared. Summaries of the subtotals of all 67 patients receiving the same drug enabled us to compare the clinical effectiveness of the three preparations.

Table 1 summarizes some of the results after the totals are divided by the total number of observations per drug. For example, 67 patients using drug Q were observed five times each day for a one-week period. The "three hours" total is, therefore, divided by $67 \times 7 = 469$. The day average is obtained by dividing all the day totals by $67 \times 7 \times 5 = 2{,}345$, etc.

Figure 2 presents the average values for table 1 in graphic form.

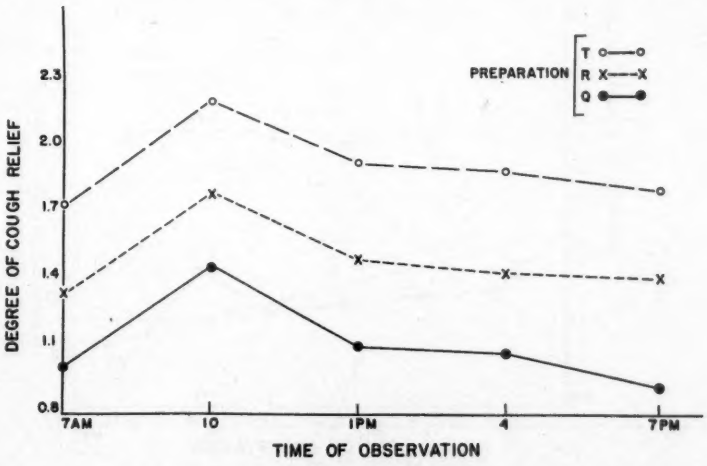

Fig. 2. Degree of cough suppression observed at different times of the day with each of three preparations.

TABLE 1

Average Cough-Suppressing Effect of Three Coded Preparations, Observed Three, Six, Nine, and 12 Hours After 7 a.m. Drug Administration and 12 Hours After 7 p.m. Drug Administration (1) Actual Time of Observation. (2) Number of Hours After Administration of Medication

Preparation	Daytime Observations					Week Average
	(1) 7 a.m.	10 a.m.	1 p.m.	4 p.m.	7 p.m.	
	(2) 12 Hrs.	3 Hrs.	6 Hrs.	9 Hrs.	12 Hrs.	
Q	1.023	1.461	1.100	.955	.876	1.083
R	1.339	1.793	1.488	1.437	1.394	1.490
T	1.740	2.220	1.940	1.881	1.808	1.918

Table 2 presents the day averages for each of the three drugs as calculated for each *day* of the week, omitting the 7 a.m. observation. The results are presented in figure 3. The straight, horizontal line through the graphs indicates the average weekly values for the 10 a.m., 1 p.m., 4 p.m. and 7 p.m. observations.

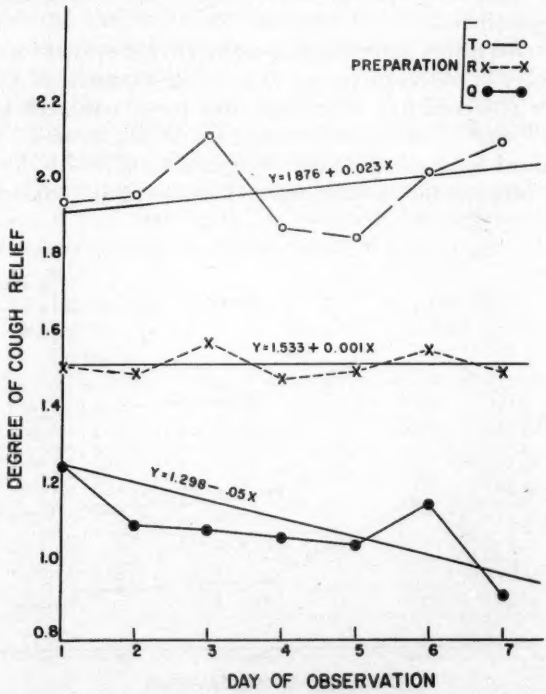

FIG. 3. Average cough suppression for the three preparations for successive days in the week.

TABLE 2

Average Cough-Suppressing Effect of Three Coded Preparations, Calculated for Each Day of Administration

(10 a.m., 1 p.m., 4 p.m. and 7 p.m. Observations)

Preparation	Day of Observation							Week Average
	1	2	3	4	5	6	7	
Q	1.254	1.112	1.086	1.082	1.056	1.175	.922	1.098
R	1.526	1.507	1.578	1.504	1.515	1.567	1.500	1.528
T	1.922	1.944	2.104	1.866	1.858	2.011	2.101	1.962

Curve fitting through the three curves Q, R and T gives the following equations to represent the best line through the points:

$$\text{Code Q} \quad Y_Q = 1.298 - .050\ X$$
$$\text{Code R} \quad Y_R = 1.533 + .001\ X$$
$$\text{Code T} \quad Y_T = 1.876 + .023\ X$$

Drug Q shows a decline in effectiveness during the seven days of observation, while drug R shows no significant variations in its effectiveness during this period of time.

T is more effective at the end of the observation period than in the beginning.

If we assume Q to be the placebo, then we may use Q as the base line for the other observations. Table 3 presents the resulting effectiveness of the remaining coded drug after the Q effectiveness for each observation is subtracted from each of the two other drugs.

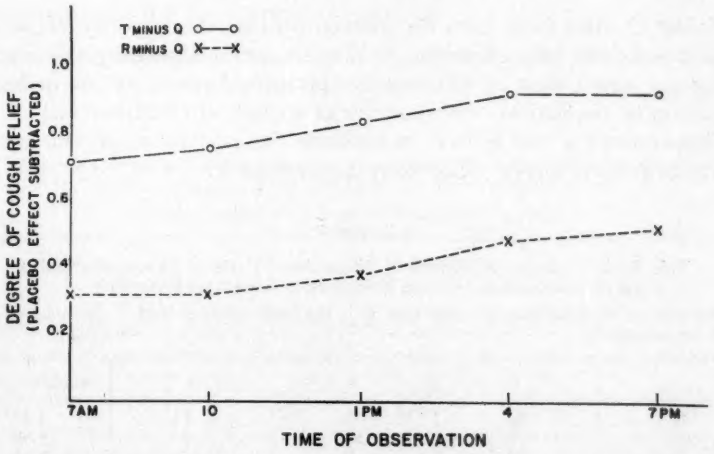

FIG. 4. Degree of cough suppression after the elimination of the placebo effect.

TABLE 3

Assuming Q to Be the Placebo, One May Subtract the Q Values to Obtain the Clinical Effect of the Two Remaining Drugs Independent of the "Placebo" Effect

	7 a.m.	10 a.m.	1 p.m.	4 p.m.	7 p.m.	Average
R minus Q	.316	.332	.388	.482	.518	.407
T minus Q	.717	.759	.840	.926	.932	.835

Figure 4 shows the resulting curves of R minus Q, and T minus Q. T, as well as R, now shows an increase in effectiveness during the 12 hours of daytime observation.

Because each patient received each drug during a period of seven days, it is also possible to compute for each patient his individual order of preference for the three coded drugs. Table 4 presents the results of this analysis. Drug Q, for example, received the lowest rating from 52 patients, and only seven patients found Q the most effective antitussive.

The "average ranking" reveals again that Q is the least effective drug and T the most effective.

Because of the large number of observations on patients who, to a large extent, serve as their own controls, it is possible to subject the data obtained to the usual statistical methods. The comparison of the day averages as well as the comparison of the hourly averages reveals in each case a highly significant difference between the three coded drugs under discussion.

Table 5 presents the t-values of the most important comparisons.

DISCUSSION OF DECODATION BASED UPON CLINICAL STATISTICAL FINDINGS

Tablet Q must have been the placebo because the majority of patients found it to be the least effective. It also showed a decreasing effectiveness during the seven days of observation, probably because of an increasing realization by the patients and observer of its lack of effectiveness.

Preparations T and R have in common the capacity to provide a long-lasting antitussive effect. T is more active than R.

TABLE 4

This Table Presents the Number of Times the 67 Patients Ranked the Coded Preparations as 1 (Least Effective), 2 or 3 (Most Effective)

(The average ranking reveals again that Q is the least effective and T the most effective cough suppressant)

	1	2	3	Average Ranking
Q	52	8	7	1.35
R	9	50	8	1.99
T	6	9	52	2.66

TABLE 5

1. Tests of significance based on the average day values (daytime observations)

Preparation Compared	t-value	t-value for 6 Degrees of Freedom	
R versus Q	11.95		
T versus R	12.52		
		P = 0.05	t = 2.45
		P = 0.02	t = 3.14
		P = 0.01	t = 3.71

2. Tests of significance based on the average hourly values (10 a.m., 1 p.m., 4 p.m., and 7 p.m. observations).

Preparation Compared	t-value	t-value for 3 Degrees of Freedom	
R versus Q	10.36		
T versus R	67.38		
		P = 0.05	t = 3.18
		P = 0.02	t = 4.54
		P = 0.01	t = 5.84

Upon completion of the analysis, the code was broken to reveal the following:

Q = Placebo
R = Dihydrocodeinone-resin-complex containing 5 mg. of drug.
T = Dihydrocodeinone-resin-complex containing 10 mg. of drug.

The behavior of the dihydrocodeinone-resin-complex at 5 mg. and 10 mg. was satisfactory, and the slow intestinal release of the drug is clinically proved in this study.

Parallel to the previously described study, we also investigated the clinical effect of:

A. Dihydrocodeinone bitartrate and phenyltoloxamine citrate in solution form.
B. Dihydrocodeinone-phenyltoloxamine-resin-complex suspension on essentially the same group of patients.

Because of the obvious difference in appearance of the medications used in the first study and the liquids administered in the second study, we pre-

TABLE 6

Average Cough-Suppressing Effect of Two Coded Drugs (A and B) Observed 12 (0), Three, Six, Nine, and 12 Hours After Administration

(Administration of drugs at 7 a.m. and 7 p.m.)

Code	Time of Observation				
	* 7 a.m.	10 a.m.	1 p.m.	4 p.m.	7 p.m.
	†12 Hrs.	3 Hrs.	6 Hrs.	9 Hrs.	12 Hrs.
A	1.422	2.022	1.656	1.356	1.172
B	1.472	1.828	1.644	1.489	1.389

* Actual time of observation.
† Hours after administration.

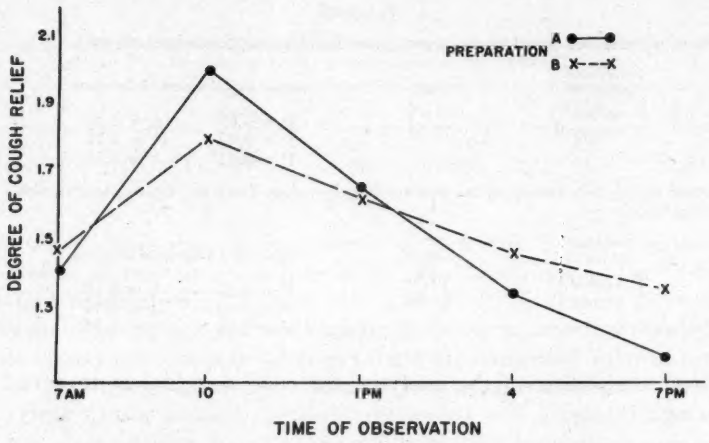

FIG. 5. Degree of cough suppression obtained with two liquid preparations.

ferred to analyze the data of the second investigation independently of the previous one.

A brief study utilizing 60 patients was completed in two periods of three days each.

The coded drugs A and B were given at random sequence to all patients, each for three consecutive days. Administration was at 7 a.m. and 7 p.m. Observations were made as described above for the previous study, at 7 a.m., 10 a.m., 1 p.m., 4 p.m. and 7 p.m. A total of 1,800 observations was made. Table 6 presents the average cough-suppressing effect of the two liquid preparations A and B as calculated for time of observation. Figure 5 presents these figures in graphic form. The 10 a.m. top of A is higher than that of B, while B seems to have a longer lasting effect than A.

To test the significance of the difference in shape of the two curves, we compared the 7 a.m., 10 a.m., 1 p.m., 4 p.m. and 7 p.m. points by applying the t-test to the 60 individual A and B observations at the various times of observation (table 7).

TABLE 7

Test of Significance of Differences Between Results Obtained with Nonresinated and Resinated Antitussive Liquids

Time of Observation				
7 a.m.	t = 1.21	P	.05	.02	.01
10 a.m.	t = 2.11	t	2.00	2.38	2.65
1 p.m.	t = .60	Degrees of freedom = 59			
4 p.m.	t = 1.32				
7 p.m.	t = 2.12				

These results at the 0.05% level of significance prove the following:

1. A slow release of drug B as indicated by the suppressed top at 10 a.m., and

2. A sustained action, as shown by superior cough-suppressing effect at 7 p.m. resulting from the single dose administered at 7 a.m.

The incidence of side-effects such as diarrhea, nausea, dizziness, etc., in both studies was exceedingly rare and was not significantly different from the incidence of side-effects observed with the placebo.

Summary

The clinical evaluation of the effectiveness of a sustained acting drug can be achieved through statistical design and frequent visits on the part of an impartial observer who assigns a value to the clinical response observed. These values can be handled statistically to demonstrate the duration-effect of the drug.

As an example of how such an evaluation may be accomplished, a dihydrocodeinone-phenyltoloxamine-resin-complex was evaluated as a long-acting antitussive. As a result of 8,835 individual observations on groups of 67 and 60 patients, respectively, receiving different drugs for periods of seven or three days each, statistical comparisons were made between resinated and nonresinated preparations.

From this study it has been shown statistically that the ion exchange resin form of dihydrocodeinone and phenyltoloxamine produces an effective antitussive which acts for approximately 12 hours.

Summario in Interlingua

Le disveloppamento de agentes therapeutic in formas longemente active presenta un numero de problemas in lor evalutation clinic. Tanto le efficacia del droga como etiam le factor de tempore debe esser prendite in consideration. Le presente reporto monstra que le evalutation clinic del efficacia de drogas a activitate sustenite pote esser effectuate per medio de un methodologia statistic que require frequente visitas del parte de un observator impartial. Le valores obtenite pote esser manipulate statisticamente pro demonstrar le duration del effecto producite per le droga.

Es presentate un exemplo de iste genere de evalutation. Il se tractava del studio del efficacia perdurative de un nove combination medicamentose de dihydrocodeinona con phenyltoloxamina in le forma de lor complexos resinose e usate como agente anti-tussitori. In iste investigation, 8.835 observationes individual esseva facite in 127 patientes, dividite in duo gruppos (de 67 e 60 individuos) recipiente differente drogas durante periodos de septe o de tres dies. Le patientes suffreva de tusse chronic in consequentia de tuberculose, chronic infection respiratori, etc. Le observationes esseva facite a intervallos de tres horas e notate in specialmente preparate formulares. Le grado de suppression del tusse esseva exprimite per le cifras ab 0 a 4, con 0 como indication de nulle effecto e 4 indicante le absentia complete de tusse durante le intervallo que precedeva le observation. Le comparationes statistic que esseva effectuate concerneva un medication fictitie, tablettas resinate e non-resinate, e preparatos liquide. Le resultato esseva un demonstration conclusive que le complexo resinose de dihydrocodeinona e phenyltoloxamina es un efficace agente anti-tussitori con un periodo de activitate de circa 12 horas.

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BRONCHOGENIC CARCINOMA COMPLICATING PULMONARY TUBERCULOSIS: A REPORT OF EIGHT CASES AND A REVIEW OF 140 CASES SINCE 1932 *

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WITHIN the last three years we have encountered eight cases of coexistent active pulmonary tuberculosis and bronchogenic carcinoma. This seemed a high coincidence of the two conditions and prompted our examination of the literature for similar experiences.

The association of bronchogenic carcinoma and pulmonary tuberculosis has been observed for over a century. Bayle (1810) has been credited with first noting the occurrence of the two diseases in the same lung, and stated that the diseases should be differentiated. Some authorities [29] feel Pinard (1846) or Schmieden gave the first true description of the associated diseases, since Bayle, in describing "phthisis cancereuse," may have attributed the phthisis due to cancer to tuberculosis, whereas only one disease existed. By 1932 Cooper [6] had collected nearly 80 cases from 40 different authors reporting the coexisting diseases. Since this time, 140 case reports have appeared in the English literature to January, 1957.

A review of the collective experience with coexisting pulmonary tuberculosis and bronchogenic carcinoma since 1932 appeared to us to have merit. This study revealed facts of clinical significance and problems in diagnosis and treatment which seemed in need of further emphasis.

CASE REPORTS

Case 1. A 68 year old housewife was first seen in September, 1953, with the complaints of a dry hacking cough which had been intermittent for 11 months, and some shortness of breath for about one year.

Physical examination was negative at this time except for early clubbing of the fingers.

Roentgen study of the chest revealed a mass approximately 4 by 5 cm. in size extending from the upper right hilar area into the upper third of the right lung. A survey radiograph of the chest taken April 1, 1951, showed a mass nearly identical with the one present at this time. One smear of the sputum for tubercle bacilli was positive; five other smears were negative. Bronchoscopy carried out on September 10, 1953, revealed narrowing of the right upper lobe bronchial orifice from extrinsic

* Received for publication August 6, 1957.
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pressure. Cytologic examination of the bronchial washings was negative, as were a smear and culture for tuberculosis.

Because of the single positive smear, the patient was started on a program of antituberculosis therapy. It was realized that the apparent stability of the lesion noted by x-ray did not favor the diagnosis of active tuberculosis or of tumor. The patient was not seen again until November 30, 1953, at which time her condition had deteriorated considerably. Significant findings were a massive right pleural effusion. Thoracentesis was performed, with the removal of 2,000 c.c. of reddish brown fluid; direct smear of this revealed acid-fast bacilli, and cytologic study also showed the presence of malignant tumor cells. Further treatment except for tuberculosis did not seem indicated.

The patient died at home approximately two weeks later. Autopsy was not performed.

Case 2. A 58 year old carpenter was admitted to the hospital on May 26, 1955. In February, 1952, a diagnosis of pulmonary tuberculosis, moderately advanced, was made both by radiographic examination and by positive smear and culture of the sputum. The patient refused treatment at that time and had returned to work. In February, 1955, he noted an increase in weakness and fatigability, and had a weight loss of about 12 pounds. Sputum examination for tuberculosis at this time was positive. Radiographs revealed a fibrotic nodular infiltration in both upper lobes, and an irregular infiltration in the right paracardiac area. He was treated at a private sanatorium for three months with streptomycin and para-aminosalicylic acid (PAS). Under this regimen the infiltrate in the upper lobes cleared considerably, but there was no alteration in the right cardiophrenic mass, considered to represent collapse of the middle or lower lobes (figure 1). Bronchoscopy showed occlusion of the right lower lobe bronchus, biopsy of which revealed squamous cell carcinoma. Some concern was felt that the soft rounded lesions in the left upper lobe might represent metastatic deposits rather than tuberculosis. Their slight regression under chemotherapy and their location at the periphery of the lobe were considered to favor tuberculosis.

On June 21, 1955, a right pneumonectomy was performed. The specimen showed squamous cell cancer, Grade II, in the lower lobe bronchus, with an abscess occupying much of the substance of the lobe. The upper lobe showed nodular and fibrotic tuberculosis. Hilar lymph nodes showed no evidence of cancer or of tuberculosis.

Postoperatively the patient made an uneventful convalescence. He was maintained on streptomycin, PAS and isoniazid (INH) for about one year. Five sputum cultures have been negative for tuberculosis. Radiographically, the lesions in the left upper lobe have remained stable. He has been capable of moderate activity without shortness of breath. A small localized empyema was drained on March 20, 1956. Recurrent cancer became evident in late 1956.

Case 3. A 51 year old white male was admitted to the hospital in July, 1955, because of a progressive infiltration in the right lung despite antituberculosis therapy. He had been admitted to the State Tuberculosis Sanatorium in July, 1954, because of pulmonary tuberculosis, moderately advanced, confined to the right upper lung. Sputum was positive on direct smear for tuberculosis. He had noted a nonproductive cough, weight loss and fatigability for several months prior to this time. Treatment at this time consisted of streptomycin, INH, PAS and modified bed-rest. He continued to have a persistent cough despite general improvement and weight gain. By serial roentgen examinations, a shadow in the region of the right middle lobe became progressively denser (figure 2), although the lesions in the apex appeared to be clearing. The patient left the sanatorium against advice on April 5, 1955.

FIG. 1. *Case 2.* Radiograph of chest, June 2, 1955.

He was seen subsequently in June, 1955, with the same complaints. Smear and culture of the sputum for tuberculosis were negative at this time. The mass noted in the region of the right middle lobe by radiographs had increased in size (figure 3).

Bronchoscopy performed in July, 1955, demonstrated a granular stenosis of the right middle lobe bronchus, biopsy of which revealed squamous cell carcinoma. On July 14, 1955, right pneumonectomy was carried out. The specimen demonstrated pneumonitis and atelectasis of the middle lobe due to a fairly well localized cancer in its bronchus. In the upper lobe there was nodular, fibrotic tuberculosis. The mediastinal glands were negative for tuberculosis and cancer. The patient was maintained on streptomycin and PAS postoperatively for about nine months. He remains free of cancer and active tuberculosis to date, although he developed a postoperative bacterial empyema which required prolonged drainage and thoracoplasty.

Case 4. A 44 year old unemployed railroad worker was admitted to the hospital in January, 1956, with a six months' history of cough, pain in the right side, and minimal exertional dyspnea. In October, 1951, he had been injured and had fractures of five ribs in the left chest, but recovered uneventfully. Eight to nine months later he developed cough, fever, weakness and mild dyspnea. His local physician obtained a positive smear for tuberculosis, for which he was admitted to the State Sanatorium in July, 1952. Sputum was positive for two of eight subsequent examinations. He was placed on streptomycin and INH. Pneumoperitoneum was initiated on September 1, 1952. The patient left the sanatorium against medical advice on January 19, 1953. The pneumoperitoneum was continued by his own physician for an additional five months, and the patient had remained clinically well and the sputum negative until the present illness.

At the time of hospital admission physical examination was essentially negative except for diminished breath sounds and coarse râles over the lower half of the right chest. Bronchoscopy revealed an infiltrating tumor in the region of the middle lobe bronchus which on biopsy showed squamous cell carcinoma. Sputum examinations for tubercle bacilli at this time were all negative. Radiograms of the chest

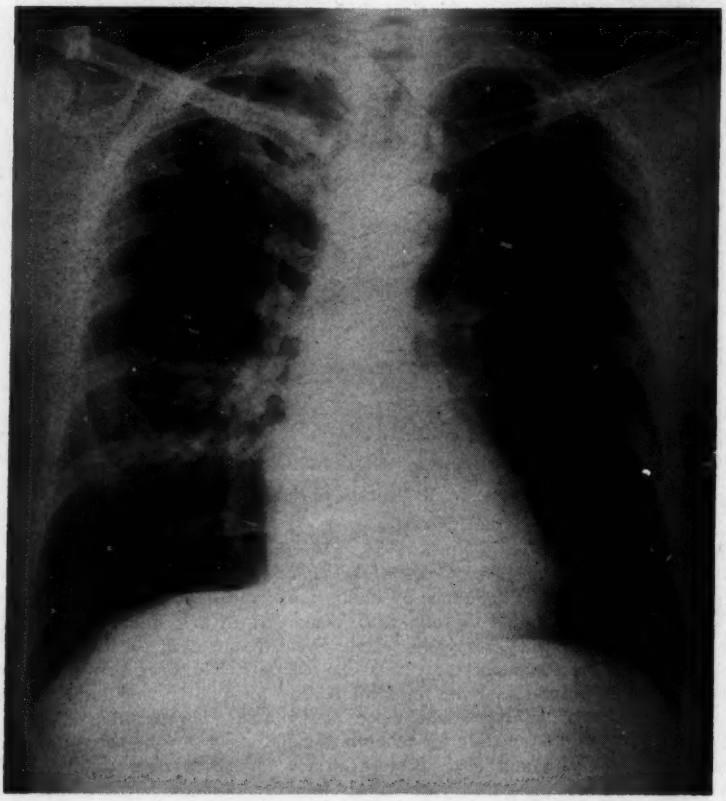

FIG. 2. *Case 3.* Radiograph of chest, June 25, 1954.

(figures 4 and 5) showed a hazy, irregular density in the medial half of the right midchest.

Right pneumonectomy was performed on January 4, 1956. The patient made an uneventful convalescence and has remained well to date. The irregular nodular density in the left upper chest has continued to be stable. The patient was maintained on streptomycin and INH for six months following surgery. Sputum examinations postoperatively have been negative for tubercle bacilli.

Case 5. A 67 year old unemployed male was admitted to the hospital in May, 1956, because of a lesion in the right lung which had been increasing in size since December, 1955. He had had diabetes mellitus for 10 years. In 1951 the patient had been hospitalized for congestive heart failure and was given diuretics and digitalis, with good effect. He had been on digitalis intermittently since, but he remained moderately short of breath on exertion. The patient was a heavy cigarette smoker, and in the past had consumed at least one quart of whiskey daily for at least 10 years. In December, 1955, he consulted his local physician because of a "cold." There had been no change in a chronic cough of 20 years' duration. Radiographic examination of the chest revealed multiple calcified nodules up to 0.5 cm. in size in

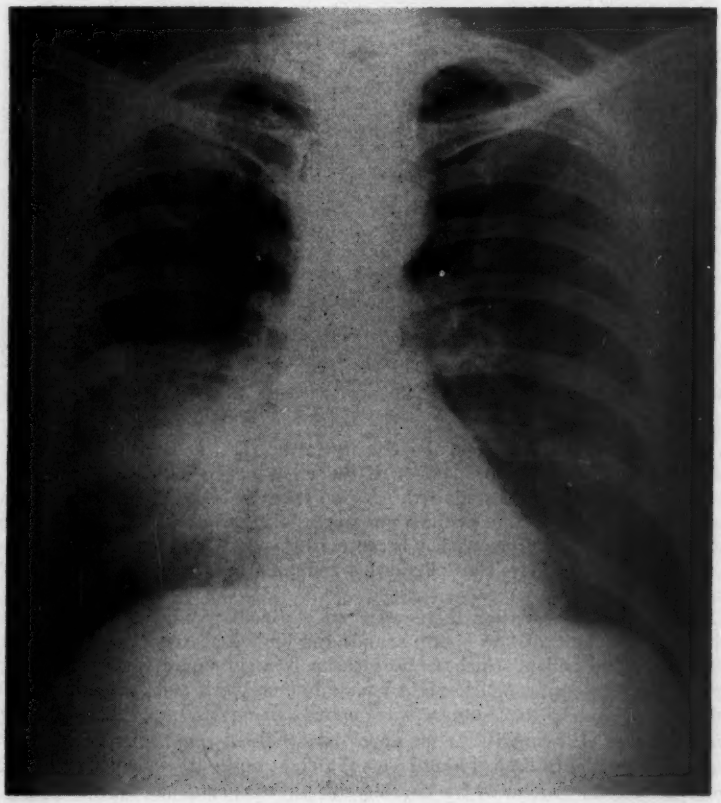

FIG. 3. *Case 3.* Radiograph of chest, April 26, 1955.

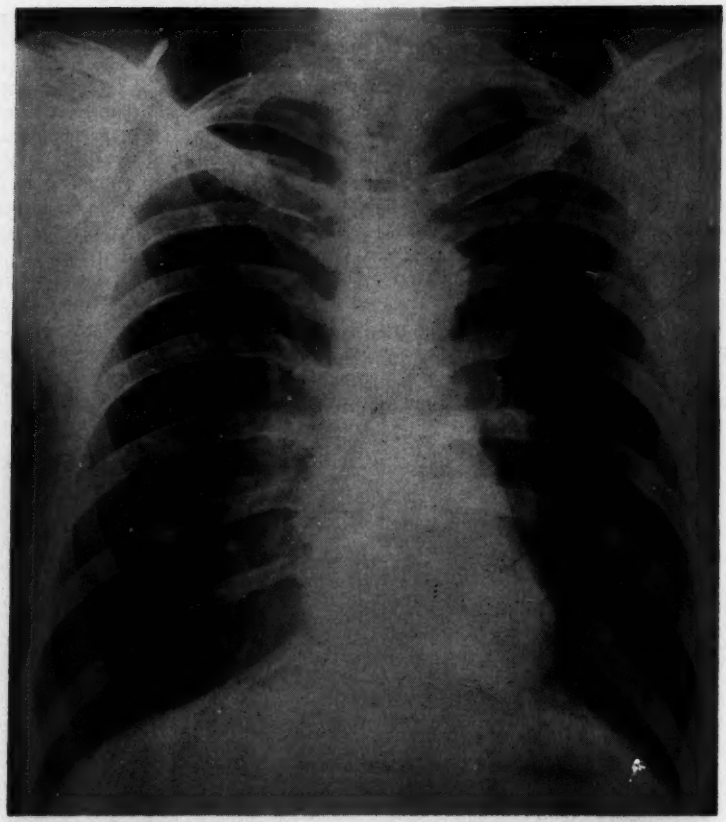

FIG. 4. *Case 4.* Radiograph of chest, May 20, 1954.

both lung fields, a stranded, irregular density in the right apex, and a rounded, noncalcified mass in the anterior portion of the right upper lobe (figure 6). Repeat examination of the chest was advised. A film taken in April, 1956, showed that the lesion in the anterior portion of the right upper lobe had doubled in size (figure 7). Removal of this was recommended because it was felt it represented a neoplasm. At this time the local physician obtained a sputum which was positive for acid-fast bacilli.

At the time of admission there were no pertinent physical findings except for barreling of the chest, distant breath sounds and limited chest motion consistent with emphysema. The patient's diabetes was easily brought under control. An electrocardiogram indicated incomplete right bundle branch block and auricular fibrillation.

Right exploratory thoracotomy was carried out on May 25, 1956. Because the tumor mass was well confined to the upper lobe without gross hilar adenopathy, and because of the patient's limited lung reserve, a right upper lobectomy was carried out. Postoperatively the patient had a considerable subcutaneous emphysema and a moderate tension pneumothorax following removal of the chest tubes on the fourth post-

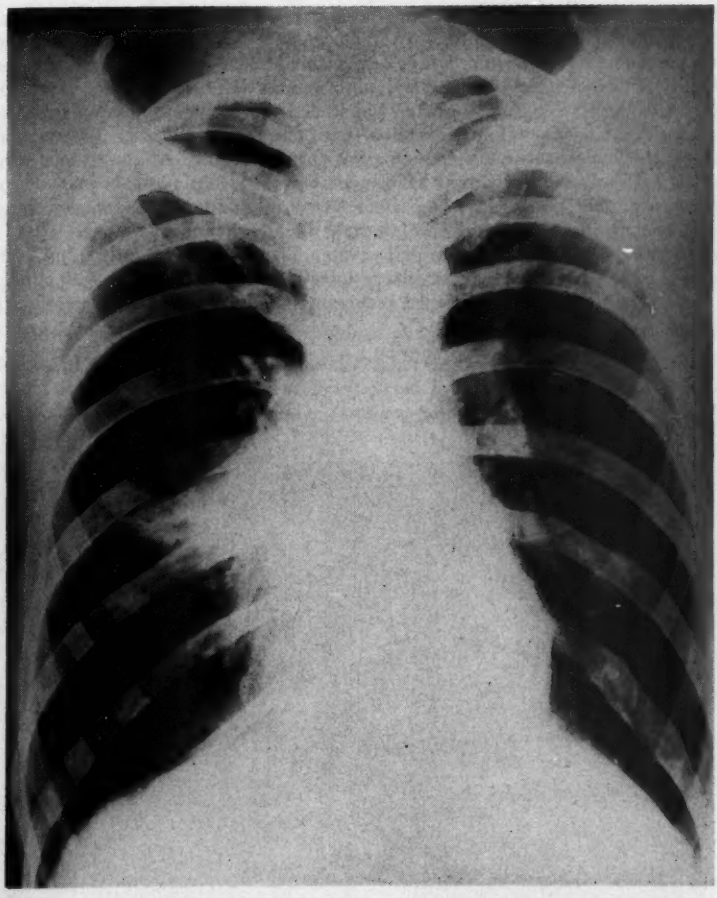

FIG. 5. *Case 5.* Radiograph of chest, December 15, 1955.

operative day. This responded to further underwater seal drainage of the pleural space. On the tenth postoperative day a dehiscence of the superficial layers (skin and subcutaneous fat) occurred. This was managed successfully by prompt secondary closure. The patient was dismissed from the hospital on the twenty-ninth postoperative day. At this time he was feeling well and had no more shortness of breath than preoperatively.

Pathologic examination of the surgical specimen revealed a Grade IV bronchogenic carcinoma in the anterior segment of the lobe, multiple small caseous granulomata through the lobe, and a necrotic abscess cavity at the junction of the apical and posterior segments. Culture of the contents of this cavity gave a luxuriant growth of *Mycobacterium tuberculosis.* Because of this finding the patient was admitted to the State Tuberculosis Sanatorium for therapy. He has remained well to the present time and has received chemotherapy for tuberculosis for one year.

Case 6. A 58 year old male was seen in July, 1956, because of malaise and loss of appetite for three months. In January, 1954, he had been admitted to the State Tuberculosis Sanatorium, where active tuberculosis was diagnosed and treated for nine months. He was re-admitted nine months later for a reactivation of his disease, with positive sputum. During his second sanatorium admission he improved symptomatically, with sputum conversion, until the present illness. A progressively enlarging shadow was seen in the superior portion of the left lower lobe (figures 8 and 9). Physical examination at this time was within normal limits. Sputum was now negative to acid-fast bacilli on smear. Laminagrams revealed irregular cavitary lesions in the apex of the left lung in addition to the tumor mass. Left pneumonectomy was carried out in July, 1956. The specimen revealed squamous cell carcinoma of the lower lobe and cavitary tuberculosis of the apex. The patient did well for a few months, but developed recurrent cancer and died nine months following surgery.

Case 7. A 56 year old white male was admitted to the hospital in November, 1956, with a one-month history of hemoptysis, anorexia and weight loss. A Public Health chest radiogram two weeks prior to admission was abnormal, and he was

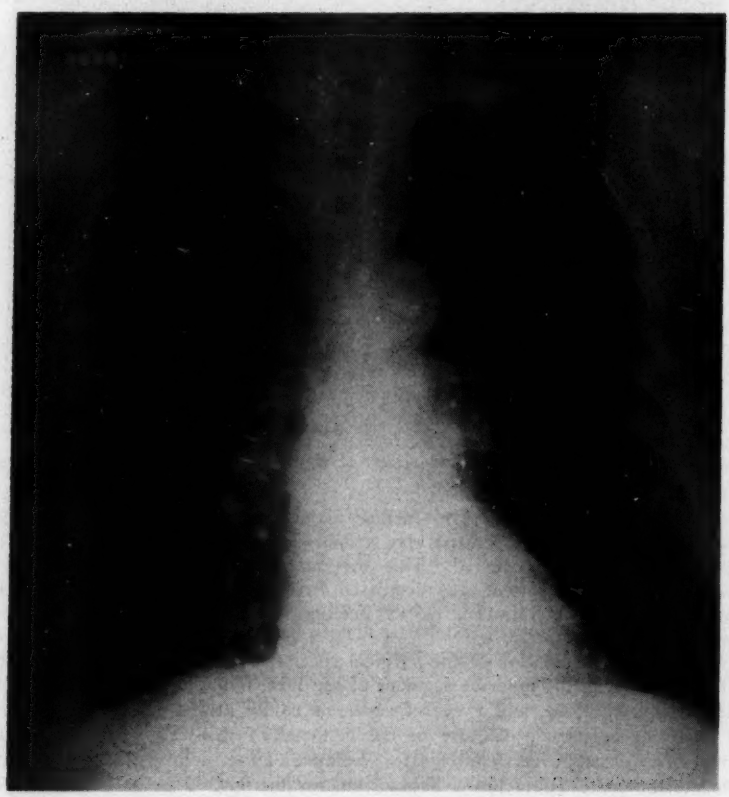

FIG. 6. *Case 5.* Radiograph of chest, December 9, 1955.

treated for five days with penicillin and re-x-rayed. The findings were the same, and he was referred for further study.

Past history revealed that he had been a chronic alcoholic.

Physical examination revealed evidence of recent weight loss. Examination of the chest was normal except for decrease in breath sounds generally.

Liver function studies were abnormal and compatible with portal cirrhosis as confirmed by needle biopsy. Sputum was positive for acid-fast bacilli on five occasions. Sputum cytology was reported as equivocal. Bronchoscopy was negative.

The patient was started on antituberculosis treatment with streptomycin and PAS on December, 1956. In March, 1957, because of persistence of the density in the right lower lung (figure 10), a thoracotomy was done. Because of the questionable pulmonary reserve of the patient it was felt advisable to do only a right lower and middle lobectomy. The surgical specimen showed squamous cell carcinoma in the central portion of the lower lobe with interlobar lymph node metastases. The patient was transferred to the State Tuberculosis Sanatorium for additional

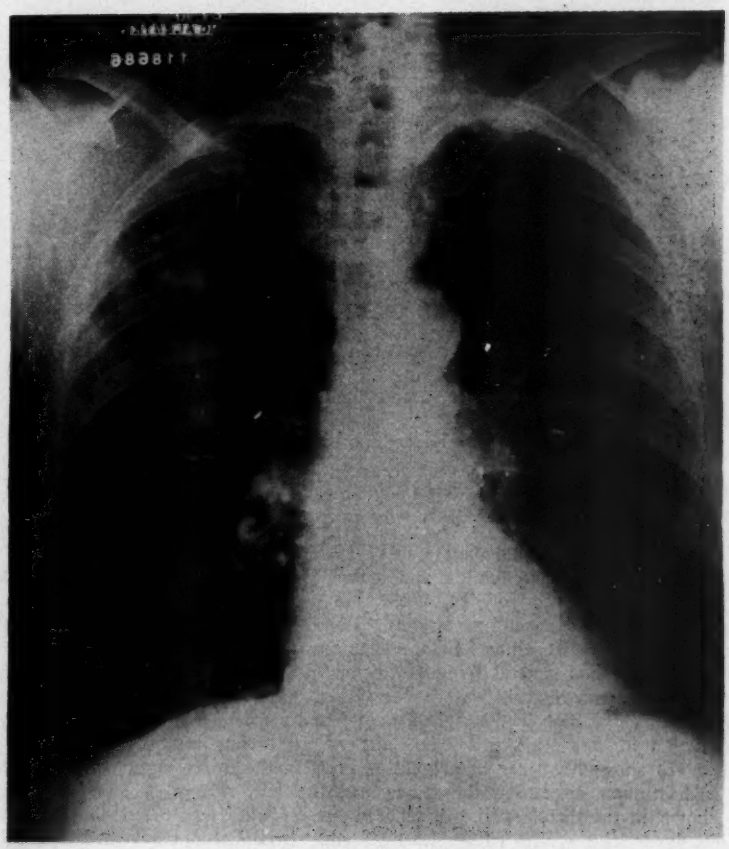

FIG. 7. *Case 5.* Radiograph of chest, April 27, 1956.

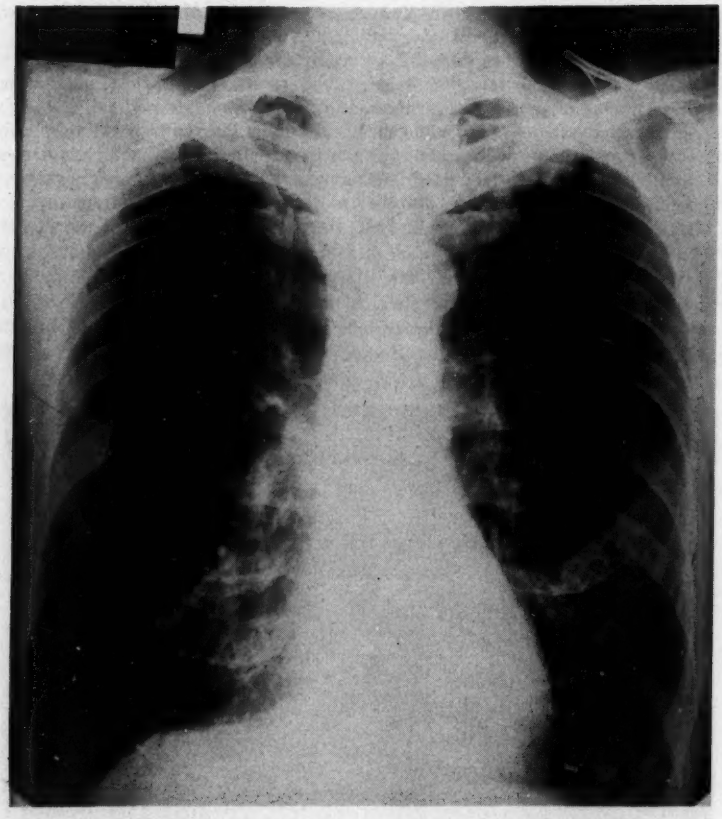

FIG. 8. *Case 6.* Radiograph of chest, March 15, 1955.

antituberculosis therapy three weeks later. His immediate convalescence has been uneventful.

Case 8. A 60 year old male was first hospitalized in July, 1955, with a diagnosis of tuberculous epididymitis and active pulmonary tuberculosis. An orchiectomy was performed on July 14, 1955. He was dismissed from the hospital July 29, 1955, while awaiting culture studies. Following positive cultures he was started on chemotherapy in November, 1955, and this was continued for 10 of the subsequent 13 months. He had several irregular dismissals from the hospital. The last positive culture for tuberculosis was in November, 1955. In April, 1957, he developed progressive aching pain in the right shoulder and a gradual loss of weight. Physical examination at this time was essentially negative, but radiographs of the chest (figure 11) showed a dense homogeneous mass in the upper right chest adjacent to the mediastinum, displacing the trachea to the left. Early osteoarthropathy was also shown in the distal radii. A tuberculous infiltrate was noted as previously in the left upper lobe, with a cavity 1.5 by 3 cm. Bronchoscopy revealed tracheal displacement to the left and mucoid secretions issuing from the right upper lobe bron-

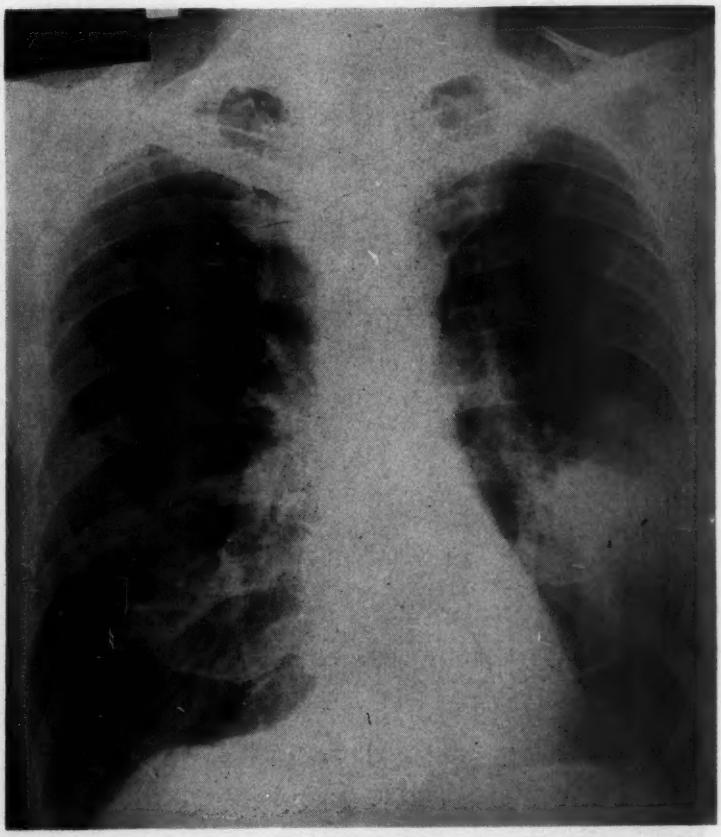

FIG. 9. *Case 6.* Radiograph of chest, June 27, 1956.

chial orifice. Right scalene lymph node biopsy was negative. Exploratory thoracotomy on June 11, 1957, showed carcinoma involving the apical chest and mediastinum which was completely nonresectable. The biopsy report was undifferentiated carcinoma. The immediate postoperative course has been satisfactory, but the patient continues to complain of right upper chest and shoulder pain, for which he is receiving radiation therapy.

MATERIAL

A summary of information obtained from the 140 recorded cases [1-3, 5, 7-9, 11-14, 16-19, 22, 23, 25, 26, 29-33] * in the English and American literature subsequent to 1932 to January, 1957, with the addition of our own eight cases, is given in table 1.

* Cases of Graham,[15] Hennell [20] and Valaitis,[34] and cases 9–15 of Drymalski and Sweany [9] and cases 3, 5, 10 of Helm and Moon [19] have been omitted because of insufficient evidence for the coexistence of tuberculosis with cancer.

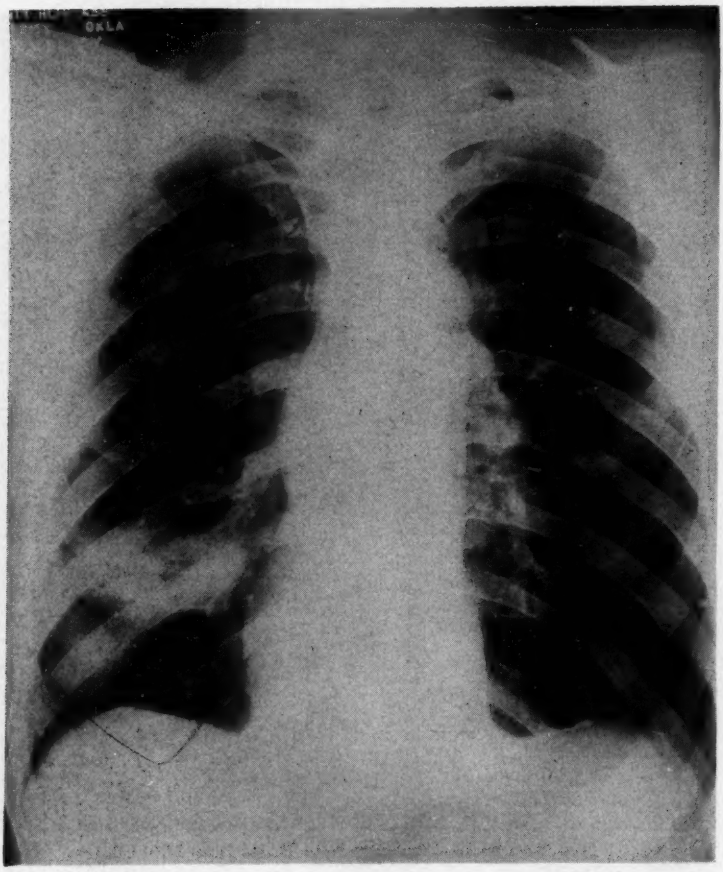

FIG. 10. *Case 7.* Radiograph of chest, November, 1956.

Of the 148 cases, all but six occurred in males. The average age of these patients was 55.2 years, and only six were below 40 years of age. These age and sex data are representative of bronchogenic carcinoma uncomplicated by pulmonary tuberculosis.

The type and distribution of tuberculosis in these combined cases were difficult to determine, since not all reports included adequate radiographs or pathologic information. However, the tuberculosis seemed to be of the usual pattern: it was dominant in the upper and posterior lung fields, and in most instances was bilateral. It also seemed most often fibrocaseous or nodular (76 cases) or fibrotic in type (25 cases), which would suggest tuberculosis of some chronicity. Ulcerative tuberculosis was described in three, exudative disease in seven, caseous in 16. The type of tuberculosis

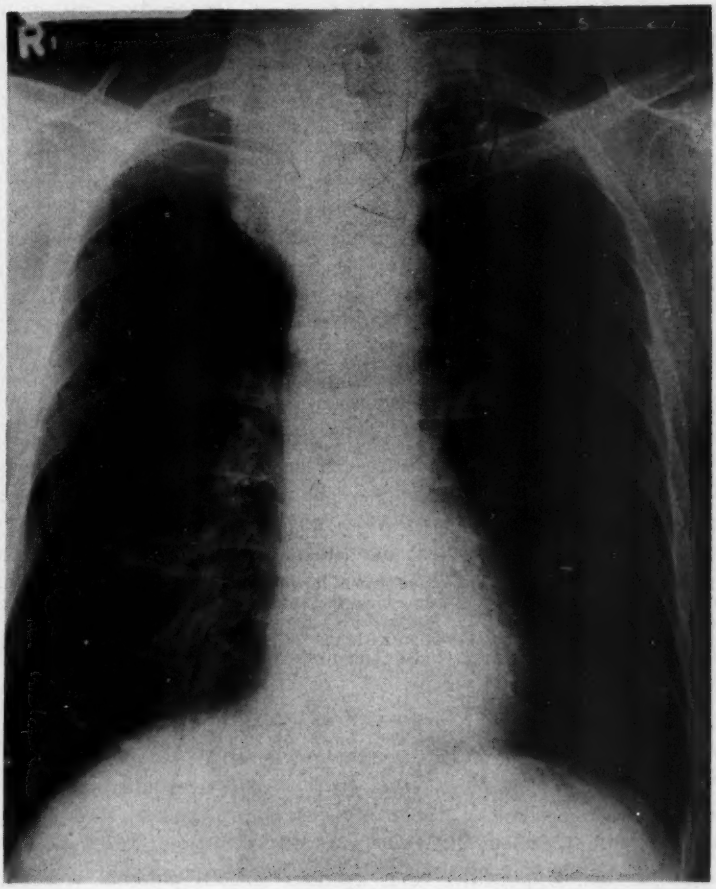

FIG. 11. *Case 8.* Radiograph of chest, May 27, 1957.

was not stated or could not be determined in 21. Cavitation was demonstrated or was stated to be present in 60 patients.

The classification of the tuberculosis according to extent could also be only crudely appraised. Of 127 patients in whom the attempt could be made, we would classify 32 as showing minimal disease, 36 as showing moderately advanced disease, and 60 would be adjudged as far advanced according to present National Tuberculosis Association standards. Bacteriologic information was provided in most reports. One hundred four patients had positive smears or cultures of sputum or pleural fluid within one year of the diagnosis of the associated carcinoma. Twenty-one additional patients had positive studies, but only a year or more prior to the

TABLE 1

Concurrent Pulmonary Tuberculosis and Carcinoma of the Lung
Clinical and Pathologic Data on 148 Cases

Social Information:

Sex (data known in 140)	Males 134	Females 6	Not stated 8
Age			
Average age		55.2 years	
Age range		20–29 yrs.	0 patients
		30–39 yrs.	6 patients
		40–49 yrs.	23 patients
		50–59 yrs.	68 patients
		60–69 yrs.	32 patients
		70–79 yrs.	5 patients

Tuberculosis:

Type of Disease:

Fibrotic	25
Fibrocaseous and nodular	76
Ulcerative	3
Exudative	7
Caseous	16
(With cavitation	60)
Indeterminate	**21
	148

Extent of Disease:

Minimal	32
Moderate	36
Far advanced	60
Indeterminate	20
	148

Activity of Disease:

Positive within 1 year	104
Positive over 1 year	21
Never positive	15
Not stated	2
TBC not suspected	6
	148

Bronchogenic carcinoma:

Cell types:

Squamous cell	84
Adenocarcinoma	15
Anaplastic ("oat cell")	31
Not stated as type	16
Alveolar cell	1
Bronchial adenoma	1
	148

Location to Tuberculosis:

Same part of lung	56
Same lung, but well separated	46
Opposite lung	29
Indeterminate	17
	148

Clinical Addenda:

Clubbing	22
Caval obst.	1
Pancoast	1
Rib destruct.	5
Vocal cord palsy	3
Horner's	1

Surgical Treatment:

Pneumonectomy	18
Partial lung resection	4
Exploratory thoracotomy only	5

diagnosis of the complicating lung cancer. Fifteen patients were never positive during life despite adequate examination for tuberculosis, and in most of these the tubercle bacilli were shown in postmortem tissue studies or smears. In two cases there was no statement as to bacteriologic data, and in six patients tuberculosis was not suspected prior to death.

A study of the nature of the pulmonary carcinoma gave no unexpected information. The usual types of primary lung tumors were encountered and in the same order of frequency as would be anticipated in a series comprised of over 95% males. There were 84 squamous cell carcinomas, 31 anaplastic or "oat cell" tumors and 15 adenocarcinomas; 16 were not stated as to cell type. There was one alveolar cell carcinoma, and one bronchial adenoma, both of which occurred in females. There seemed to be no particular predilection for the malignancy to appear in the zone of tuberculous activity. Of course at necropsy the cancer would be at maximal extent and

would be anatomically closer to the tuberculosis than at the time of clinical diagnosis ante mortem. In this study, derived largely from necropsy reports, the cancer occurred in the lung opposite to tuberculous activity in 29 cases, or appeared in a portion of the lung well removed from the tuberculosis in another 46 cases. In 56 instances the tuberculosis and cancer were spatially closely associated. In some cases [26, 29] there is good reason to feel that by physical extension or inanition the malignancy may cause a breakdown of preëxisting quiescent tuberculosis or allow its extension. No evidence has been produced to show the development of cancer from the wall of a chronically diseased tuberculous cavity.

Surgical therapy has been carried out in only 27 of the 147 patients. Exploratory thoracotomy alone was performed in five, segmental resection of a localized carcinoma was carried out in one, lobectomy was performed in three, and pneumonectomy was possible in 18. Four of the 16 patients who had resection of the growth are already known to have died, and the information is scant and for only a brief period postoperatively in the remainder. Three of our patients are still alive and without known recurrence, 24 months, 15 months and 13 months postoperatively, respectively. The generally low resectability and operability rate is a reflection of several factors. The difficulty or delay in diagnosis of combined disease, especially in most sanatoria, and the reluctance to carry out resections for cancer in the presence of contralateral tuberculous disease, are undoubtedly causes of the common finding at exploration of this type of bronchogenic carcinoma that the lesion is inoperable.

Discussion

The relationship between pulmonary tuberculosis and bronchogenic carcinoma remains unsettled. It has been stated variously that tuberculosis predisposes to the development of cancer, that there is an antagonism preventing their frequent concurrence, or that the two conditions coincide by chance. It is currently believed that there is neither a negative nor a positive correlation, and it is apparent that the diseases are not mutually exclusive. There is good reason to feel that this association will be noted more frequently in the future. With the increased survival of patients afflicted with tuberculosis due to effective present therapy, more patients will develop cancer of the lung later in life. When significant gross or active tuberculosis is considered, from 3.8% to 9.4% of the patients with bronchogenic carcinoma may be said to have tuberculosis, according to autopsy material. Representative of such data is the report by Neussle [26] in a collation of autopsy data from 16 authors who found active pulmonary tuberculosis in 85 of 1,335 cases with bronchogenic carcinoma, an incidence of 6.4%. The observation of bronchogenic carcinoma in autopsy cases of tuberculosis is somewhat less frequent, and this may be attributed to the greater number of females and the earlier age of death when due to tuber-

culosis. Gerstl [18] found bronchogenic carcinoma in 0.44% of 1,600 autopsy cases of pulmonary tuberculosis. Over a 20-year period Shafran and Kavee [31] found 114 cases of primary lung cancer reported among 7,847 autopsies on males and females of all ages with tuberculosis (1.45%). Many additional cases of associated bronchogenic carcinoma and pulmonary tuberculosis are included in series of either disease alone. Such cases are without clinical information for detailed study and could not be included here.

Patients with bronchogenic carcinoma and pulmonary tuberculosis have a general similarity in their clinical appearance. In either condition there may be cough, hemoptysis, fever, weight loss, dyspnea, and a variable amount of chest pain. However, there are certain differences in clinical features which should suggest a diagnostic separation of the conditions when they occur alone, or should permit the diagnosis of cancer complicating pulmonary tuberculosis. Most of these differences have been described in earlier reports. A cough which is persistent despite all medications or drugs is more common in cancer than in tuberculosis. Persistent hemoptysis, or hemoptysis which is sudden and profuse in limited pulmonary disease, is unusual in tuberculosis. In tuberculosis, hemoptysis is usually moderate and of brief duration. Unless there is extensive pleural involvement, chest pain is usually not severe or persistent in tuberculosis. Pain is often a presenting symptom in cancer, and is usually continuous, dull and progressive. Wheezing, if localized and unexplained by the degree or location of parenchymal disease, should lead to the suspicion of a bronchial lesion and the possible presence of a neoplasm. Further studies, such as bronchoscopy and cytologic examination of the sputum under any of the above circumstances, will usually allow the differentiation between endobronchial tuberculosis and bronchogenic carcinoma.

The only certain means of making a clinical distinction between carcinoma and tuberculosis is by the appearance of signs of inoperability of the cancer. Such symptoms as Horner's syndrome, clubbing of the digits, vocal cord paralysis, chest wall destruction or the presence of fixed supraclavicular nodes are all so rare in tuberculosis alone as to permit the almost certain diagnosis of bronchogenic carcinoma.

The introduction of effective antituberculosis drugs has provided a further valuable aid in the distinction between the two conditions. A failure of prompt clinical improvement or of clearing of parenchymal disease should raise the possibility of some complicating condition. Furthermore, a progression of disease clinically or radiographically despite sputum conversion should strongly suggest an intercurrent bronchogenic carcinoma.

Hauser and Glazer [18] have recently summarized the roentgen features which should alert the radiologist and clinician to the coexistence of tuberculosis and carcinoma of the lung. They emphasize that a unilateral prominence of the hilum, a hilar measurement (over-all length of both hila)

exceeding 13 cm., or paratracheal lymph node involvement, is strongly suggestive of bronchogenic carcinoma. The presence of atelectasis, or of a collapsed lobe or segment in which mottling, linear streaking and/or cavitation is not seen, in which the density is thus essentially homogeneous, is usual in bronchogenic carcinoma. Furthermore, a "spread of the disease" in which the character of the infiltration is homogeneous, and particularly if it is in the lower lung fields, should make the physician suspect cancer. A nodular density greater than 3 cm. in diameter—again if in the lower lung fields—is more suggestive of cancer than of tuberculosis. These authors made no specific note of bone destruction which should be mentioned. It is most unusual for tuberculosis, particularly in cases under present treatment, to advance to the point of destruction of the bony chest wall. Evidence of bony destruction is prima facie evidence of cancer.

The management of patients in whom acid-fast bacilli are demonstrated, in the absence of confirmatory radiographic or pathologic evidence of tuberculosis, remains difficult. A single positive smear probably may be safely disregarded, provided reasonable efforts have been made to exclude tuberculosis. Suitable cultural and guinea pig virulence studies become mandatory to exclude the presence of saprophytic, nonpathogenic acid-fast bacilli or contaminants. Repeated or confirmatory demonstration of tubercle bacilli requires appropriate chemotherapy.

Patients with active tuberculosis at the time of surgery should be treated according to current concepts of chemotherapy. The agents must be given in combination according to determined effectiveness, and for prolonged periods of time following resection. Instability of possible tuberculous foci in the remaining lung is further indication for adequate chemotherapy. From available experience, there would seem to be no great danger of reactivation of quiescent tuberculosis in the remaining lung if adequate therapy is maintained postoperatively.

If any improvement is to be effected in this group, earlier diagnosis, prompt resection of malignant disease, and effective chemotherapy will have to be accomplished in the future. That the prognosis is not hopeless is attested by the few reported successes and the results in three of our own cases.

Summary

1. One hundred forty cases of bronchogenic carcinoma complicating pulmonary tuberculosis found in the English literature between 1932 and January, 1957, have been reviewed, together with eight cases treated by the authors.

2. The combined diseases occurred in males in over 95% of the cases, and the patients were of the age group and distribution of bronchogenic carcinoma alone.

3. There were no unusual pathologic features of the tuberculosis in these patients. The tuberculosis is most often bilateral, apical or superior in

location, and is most often (65%) chronic fibroid or caseonodular in type. Twenty-eight per cent of the cases were moderately far advanced, 47% far advanced. Seventy-five per cent of patients demonstrated acid-fast bacilli within one year of the diagnosis of the combined diseases.

4. The location of the bronchogenic carcinoma in these patients bore no relationship to the tuberculosis. The lung cancer was of the usual variety and frequency of primary lung tumors.

5. There are no specific clinical differences between pulmonary tuberculosis and bronchogenic carcinoma. Quantitative differences in symptoms and findings do occur which suggest the diagnosis of either disease alone, or of their combination.

6. Failure to achieve or maintain general improvement during present-day treatment of tuberculosis in a middle aged man should suggest the possibility of complicating bronchogenic carcinoma.

7. Radiographic signs of help in the diagnosis of bronchogenic carcinoma complicating pulmonary tuberculosis are (a) unilateral prominence of the lung hilum, (b) paratracheal lymph node enlargement, (c) atelectasis, (d) nodular densities greater than 3 cm. in diameter, or (e) bony destruction.

8. Only 21 of these patients have had definitive treatment for bronchogenic carcinoma. Only by alert diagnosis and aggressive treatment can this unfavorable combination of diseases be improved.

Summario in Interlingua

Carcinoma bronchogenic occurrente como complication de tuberculose pulmonar non es incommun, ben que le association es probabilemente coincidental. Nos ha studiate le reportos de 140 casos trovate in le litteratura inter 1932 e januario 1957 e reporta detaliatemente octo casos tractate per nos mesme.

Le patientes in qui le combination del duo disordines occurreva esseva masculos in 95% del casos, e le distribution de etate esseva illo trovate in carcinoma bronchogenic non-associate con tuberculose. Le sito del carcinoma bronchogenic in iste patientes non se trovava in un specific relation anatomic con le tuberculose. Le tuberculose esseva usual in varietate e in sito. Illo esseva fibroide o caseo-nodular in 65% del casos e de grados moderatemente avantiate in 75%. Tres quartos del patientes monstrava bacillos acido-resistente intra un anno post le diagnose del combination de morbos.

Il existe differentias quantitative—tanto in le symptomas como etiam in le constatationes medical—que suggere le presentia del un o del altere del duo morbos o de ambes in combination. In particular, le non-effectuation o le non-mantenentia de melioration general in un patiente mascule de etate medie in despecto del uso de moderne methodos de tractamento pro tuberculose deberea suggerer le possibilitate del presentia complicatori de carcinoma bronchogenic. Signos radiographic que es de adjuta in le diagnose de carcinoma bronchogenic occurrente como complication de tuberculose pulmonar es (a) prominentia unilateral del hilo pulmonar, (b) allargamento de nodo lymphatic paratracheal, (c) atelectasis, (d) densitates nodular de un diametro de plus que 3 cm, o (e) destruction de osso.

Solmente 21 de iste patientes habeva recipite tractamento specific pro carcinoma bronchogenic. Le combination del duo morbos es pauco favorabile, e le resultatos

de lor tractamento pote esser meliorate solmente per alertia diagnostic e aggressivitate therapeutic. Le facto que le prognóse non es completemente desperate es illustrate per plure successos de tractamento reportate in le litteratura e per le resultatos in tres de nostre proprie casos.

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CASE REPORTS

PRIMARY HYPERPARATHYROIDISM DUE TO A PARATHYROID ADENOMA: ANTEMORTEM DIAGNOSIS WITH TERMINATION IN POSSIBLE ACUTE PARATHYROID HORMONE INTOXICATION *

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PRIMARY hyperparathyroidism was seldom diagnosed during life prior to 1925. Twenty-six of 27 recorded cases from 1903 to 1925 were diagnosed at autopsy.[1] The pioneer work of Mandl [2] in 1926, consisting in the removal of a parathyroid adenoma from a patient suffering from osteitis fibrosa cystica, with remarkable improvement, and the reported extraction of a parathyroid hormone by Collip,[3] caused an immediate upsurge in the seeking out of cases of hyperparathyroidism. The subsequent classic studies carried out by Albright and co-workers [12a, b, c, d] aided greatly in establishing hyperparathyroidism as a well defined clinical entity. A higher index of suspicion made diagnosis possible during life.

The incidence of primary hyperparathyroidism is unknown. It is generally considered quite small, but is by no means so rare as was formerly thought. The disease occurs most frequently in middle life, and slightly more than half of the patients are females. The most common cause is a parathyroid adenoma —in approximately 90% of the cases. Less often diffuse hyperplasia is found, and very rarely a carcinoma. It should be noted that in some cases no changes are found in the parathyroids themselves, but aberrant adenomata are found in the mediastinum, thyroid or thymus, a fact which makes surgery somewhat difficult on occasion. The disease is usually chronic over a period of years, and remissions of varying length may occur.[4] The onset of symptoms may be insidious. It should be suspected and ruled out in patients with urinary calculi, benign bone tumors or unexplained fractures. Early diagnosis is imperative to prevent permanent damage to the kidneys, bones and the cardiovascular system. In an occasional patient the gastrointestinal symptoms of primary hyperparathyroidism may so dominate the symptomatology that peptic ulcer is suggested, a fact emphasized by Gutman [5] as early as 1934. Recently Atlas et al.[6] have cast some doubt and presented evidence against the existence of the so-

* Received for publication December 15, 1956.

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called Burnett's syndrome, characterized by hypercalcemia without hypercalciuria or hypophosphatemia, calcinosis, ocular lesions and renal insufficiency following prolonged intake of milk and alkalis in the treatment of peptic ulcer. The authors suggest that this symptom complex in patients with peptic ulcer should direct attention to the possibility of masked hyperparathyroidism.

The disease, if suspected, is usually easily diagnosed by the characteristic clinical, x-ray and chemical findings. Unfortunately, the early symptoms rarely lead to a diagnosis. In most recorded cases, because of its rare occurrence and protean clinical manifestations, there is an unfortunate and sometimes fatal time lag between the onset of symptoms and the ultimate diagnosis. The biochemical picture in a typical case consists of hypercalcemia, hypercalciuria, hypophosphatemia and hyperphosphaturia. An increased serum alkaline phosphatase is present whenever there is bony involvement.

Primary hyperparathyroidism manifests itself in disease of the skeletal system, involvement of the urinary tract or in the symptoms of hypercalcemia. These manifestations are attributed to the excessive secretion of parathyroid hormone. Evidence of bone disease may be associated with disease of the urinary tract and varying degrees of hypercalcemia, depending largely upon the dietary intake of calcium. From a diagnostic standpoint it is important to note that in the presence of hypoproteinemia the serum calcium may be normal or low. Disease of one system may appear without detectable effects on the other. Recent investigations have shown involvement of the urinary tract to be as common as involvement of the skeleton. The hypercalciuria and hyperphosphaturia eventually cause severe renal damage, with subsequent retention of phosphate, which tends to confuse the diagnosis. With involvement of bone there is either generalized demineralization or cyst formation. One of the early signs is the absence of lamina dura about the teeth. The skull frequently has a "moth-eaten" appearance. The bones are usually tender and subject to deformities and fracture. As a result of the increased urinary excretion of calcium and phosphate there may be recurrent renal calculi, followed by infection. The diffuse deposition of calcium leads to nephrocalcinosis. Occasionally there are polydipsia and polyuria, simulating diabetes insipidus.[7] Metastatic calcifications to various organs, such as the eyes, lungs and stomach, are not infrequent.

In the majority of cases the symptoms of hypercalcemia—muscular weakness, hypotonia, nausea, anorexia, and constipation—play a secondary role. In a rare instance, however, a sudden elevation of the serum calcium may precipitate a severe episode of extreme restlessness, intractable vomiting, tachycardia, prostration, coma and death, a condition known as acute parathyroid intoxication, similar to that observed in animals given excessive doses of parathyroid hormone.[8]

The case to be presented falls into the latter group, the so-called acute parathyroid intoxication, a rare complication of hyperparathyroidism. A review of the literature reveals only about 10 reported cases. The mechanism of parathyroid intoxication is very probably responsible for many unexplained deaths. The scarcity of reports may be due to the fact that the parathyroid glands are seldom investigated in postmortem examinations.[8] Our patient with a parathyroid adenoma on the lower pole of the right thyroid lobe had a clinical remission lasting six years. The diagnosis was made ante mortem and confirmed at autopsy. The mechanism of death resembled that seen in parathyroid intoxication.[9]

Case Report

A 25 year old white female complained of increasing fatigability, anorexia and listlessness for three months prior to her first hospitalization in 1947. She recalled that at the age of 13 she had been overweight and anemic, and had been treated with iodides, although she had had no goiter. She believed that she improved after a few months. There had been no pregnancies except for a miscarriage in 1945. With the onset of fatigue she felt a small mass in the throat. She lost about 20 pounds, and at times was keyed up and anxious. Her menses were regular each month, but the flow had diminished recently. For two weeks before this first hospital admission she had been taking 10 drops of Lugol's solution three times a day.

Examination revealed a thin, nervous young woman with a slight tremor of the tongue and outstretched hands. Blood pressure readings were 206 mm. and 200 mm. of mercury systolic, and 110 mm. diastolic, with a regular pulse of 140 per minute. The pulmonic second sound was increased. There was no exophthalmos. On the right side of the neck in the region of the thyroid gland, above the supraclavicular joint, a firm, smooth mass, 2 cm. in size, moved with swallowing.

Laboratory reports included basal metabolic rates of plus 5% and plus 13%, with a serum cholesterol of 227 mg.%. Nonprotein nitrogen, 37 mg.%. Oral glucose tolerance curve: 77–115–161–131–120–125. Hemoglobin, 13.6 gm.; white blood cells, 9,300; polymorphonuclears, 59%; lymphocytes, 38%; monocytes, 2%; basophils, 1%. Urinalysis: showed a specific gravity of 1.006 and a trace of albumin. An electrocardiogram showed a sinus tachycardia (rate, 130 per minute). Three weeks later an electrocardiogram revealed a second degree heart block. A chest film showed displacement of the trachea slightly to the left at the base of the neck. On a skull film the bones of the vault showed rather marked granular appearance (figure 1).

The patient was treated for a possible thyroiditis with thiouracil, 0.3 gm., for five days, after which the neck in the region of the thyroid became markedly swollen and the patient experienced dysphagia. Shortly after the drug was stopped both the choking and the swelling subsided. The patient felt much better and was sent home. Except for a normal pregnancy and delivery the next year, and the extraction of all of her teeth for dental reasons, she remained well for approximately the next six years.

On November 16, 1952, the patient was admitted to Lebanon Hospital with several weeks' history of conjunctivitis, photophobia, pains in the left knee, an 18 pound weight loss, ankle edema, tachycardia, weakness and an intermittent fever ranging to 101° F. The pertinent physical findings in this 31 year old asthenic woman included a sinus tachycardia of 120/min. and a blood pressure of 180/96 mm. of Hg. Above the right supraclavicular joint, in the region of and part of the lower pole of the thyroid, was a firm, smooth, nontender nodule about 4 cm. in diameter. The ophthalmologist reported an irregular calcium deposit along the limbus, episcleritis, and obscure choroidal lesions manifested by numerous pale pink, poorly defined areas of varied shape which lay underneath the retinal vessels.

Hemoglobin was 9 gm.; white blood cells, 14,400, with polymorphonuclears, 76%; lymphocytes, 16%; mononuclears, 8%; red blood cells, 2,950,000; fasting blood sugar, 109 mg.%; urea, 19 mg.%; total protein, 5.5, with albumin, 3.0, and globulin, 2.5. Urinalysis showed a specific gravity of 1.008, with 2 plus to 4 plus albumin, occasional hyaline casts, and 1.009 on concentration test. Congo red gave 14% absorption; basal metabolic rates varied from plus 18% to plus 38%. Serum cholesterol, 160 mg.%.

Differential diagnosis included thyroiditis, toxic thyroid adenoma and collagen disease. When the skull film of 1947 was made available a presumptive diagnosis of primary hyperparathyroidism due to parathyroid adenoma was entertained. On

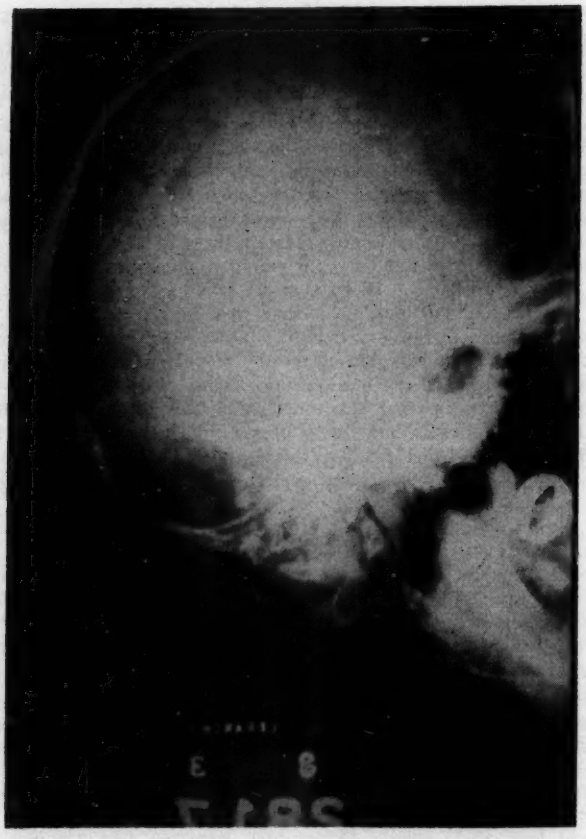

FIG. 1. Skull x-ray, 1947.

December 10, 1952, the serum calcium was 17.6 mg.%; phosphorus, 3.3 mg.%; alkaline phosphatase, 25.7. Repeated studies gave serum calcium, 17.7 mg.%; phosphorus, 2.9 mg.%; alkaline phosphatase, 24.1; Sulkowitch, 2 plus; urinary calcium excretion, 116 mg./1,250 c.c.; uric acid, 3.6 mg.%. X-ray of the chest revealed no pathologic process. A skull film on December 12, 1952, revealed the entire vault to be riddled by large and small osteolytic lesions (figure 2). Further studies of the skeletal system showed numerous small stippled areas and translucencies of the phalanges, metacarpals, ulna, radius, humerus and femur. X-ray of the knees showed small lytic areas in the bones, with thinning in vascular areas on the cortex and multiple small areas of rarefaction. Intravenous pyelograms were negative for calculi or calcifications.

By the end of December both knees had become swollen and painful, while the submaxillary glands had markedly enlarged and were of very firm consistency. The patient's course was rapidly downhill. Biopsy of the right submaxillary gland under general anesthesia was performed on December 31, 1952, but the patient never regained consciousness.

FIG. 2. Skull x-ray, 1952.

Postmortem examination by Dr. J. Ehrlich demonstrated a parathyroid adenoma, 1.5 cm. in diameter, near the lower border of the right thyroid lobe; the three other parathyroids were normal. The heart was firmly contracted. Chalklike material was seen in several irregular areas of the left atrium, and fine whitish crystals were present in the renal pyramids and cortices. Thin white plaques of calcium were seen in the renal, iliac, splenic, mesenteric and other arteries. There was extensive demineralization of the bones. Calcinosis of the submaxillary glands was marked. Incidental findings were a cherry-sized hepatoma in the left lobe of the liver and an antemortem thrombosis of the left main renal and ovarian veins.

DISCUSSION

The exact physiology of parathyroid hormone in the regulation of calcium and phosphorus concentrations in body fluids has not been clearly defined. Parathyroid activity does not appear to be under the direct control of a pituitary tropic hormone; however, an indirect relationship to other endocrine glands has been observed experimentally. Adrenocorticotropin, growth hormone and adrenal steroids cause hyperplasia, whereas hypophysectomy causes involution of

the parathyroids.[10] It is generally agreed that parathyroid hormone production is stimulated by a fall in the concentration of the serum inorganic calcium. There is less convincing evidence that a high serum phosphorus in the absence of hypocalcemia will stimulate parathyroid activity.

Parathyroid hormone in physiologic doses has been shown to produce the following sequence of events: (1) an increase in urinary excretion of phosphorus; (2) a decrease in serum phosphorus; (3) an increase in serum calcium level; and (4) an increase in urinary excretion of calcium. In excessive amounts these effects are exaggerated and produce, in addition, a prolongation of systole and a shortening of diastole of the heart, a dilatation of the visceral vessels and increased tonicity of the gastrointestinal tract.[11]

Albright [12] believes these changes are due primarily to the action of parathormone on the kidneys by lowering the renal threshold for the excretion of phosphorus. The resultant hypophosphatemia causes a rise in serum calcium in order to maintain the calcium-phosphorus product as nearly a constant as possible. The hypercalcemia is followed by hypercalciuria. In order to keep the calcium level elevated, the bones mobilize calcium phosphate. This in turn results in fibrocystic disease, depending upon the dietary consumption of calcium. If the demand for calcium is met by dietary intake there is little or no resorption of bone. Albright also postulates a direct action of the hormone on bone. The mechanism of release of calcium in response to parathyroid hormone is not clearly understood. It does not seem to be due to stimulation of osteoclasts, but rather to a direct effect on matrix, as suggested by Carnes.[13]

Selye,[14] on the other hand, has shown that parathyroid hormone exerts its effect on serum calcium primarily by its direct action on bone, rather than on the kidneys. Recently Grollman's [15] experiments with nephrectomized dogs have seemed to bear out the earlier work of Selye. Munson,[16] working on parathyroidectomized rats, found the parathyroids to maintain the blood calcium level by a mechanism independent of the kidney, presumably directly on bone. He postulated a calcium-mobilizing activity and a phosphaturic activity. He could partially separate these two activities. Zondek[17] stated that there may be no single factor in osteitis fibrosa, since other endocrine glands affect mineral metabolism.

It is generally agreed that the pathologic physiology of primary hyperparathyroidism is the direct result of parathormone overproduction. The blood chemical picture and the urinary findings are exactly the same as those observed in experimental hyperparathyroidism in animals.[18] Collip [8] described his experiments with dogs as follows: "experimental parathormone overdosage causes in order vomiting, diarrhea, uneasiness. When maximum serum calcium of 20 mgs.% is reached, depression and respiratory distress occur. The serum calcium begins to fall, there is more vomiting and passing of blood per rectum, then collapse. The blood phosphorus rises abruptly as does the blood urea and nonprotein nitrogen. Death follows in a few hours. There is a marked decrease in blood volume, a characteristic thickening of the blood, and decreased coagulation time. At first there is a compensated alkalosis followed by a compensated and then uncompensated acidosis just prior to death. The kidneys practically cease to function abruptly about the time the serum calcium has reached its peak. Postmortem there is marked congestion of the alimentary canal with the presence

of blood in the stomach and intestines. Hypercalcemia, hyperphosphatemia supervene, and terminally acidosis."

Hueper's [19] observations on the effects of excessive amounts of parathormone in dogs revealed that the diastole of the heart became more and more incomplete, the pulse slow and irregular. The blood pressure dropped considerably. There were multiple thrombi in the small vessels and capillaries of the myocardium, extreme dilatation of the vessels of the internal organs and extensive intensification of the tonus of the stomach and intestines, causing vomiting and diarrhea. Due to the highly increased blood calcium, the coagulability of the blood was augmented and caused the formation of thrombi and secondary hemorrhage in the hyperemic organs.

Cantarow, Stewart and Housel [20] believe that the degeneration and necrosis in the myocardium, kidneys, stomach, thyroid, liver and skeletal muscles are due to a direct toxic effect of the parathyroid hormone.

Hyperparathyroidism, as we pointed out earlier, may in some cases manifest itself in the symptoms and signs of hypercalcemia, with dangerous sequelae. There are a decrease in the excitability of nervous tissue and a tendency to metastatic calcifications, interfering with the vital functions of various organs. In rare instances of hyperparathyroidism, the symptoms of hypercalcemia dominate the picture and may cause sudden and unexpected death. This syndrome is known as acute parathyroid poisoning, or "hyperhyperparathyroidism." [8] This rare and dangerous complication, in the few reported cases, usually occurred when the serum calcium rose to a level higher than 17 mg. per 100 ml. A failing renal function and a rising serum calcium constitute the danger signals. Prompt administration of intravenous fluids to combat hemoconcentration, followed by immediate parathyroid surgery, seem to be the only choice of therapy in this syndrome.

In our case the patient remained well for almost six years after the onset of symptoms referable to the parathyroid adenoma. Both Zondek [17] and Snapper [4] remark on the long-lasting remissions in this disease but the absence of spontaneous cures. Our patient most probably died of acute parathyroid intoxication; this followed biopsy of the submaxillary gland, an innocuous procedure. It is therefore apparent that no surgery, no matter how minor, should be attempted in such cases, unless one is prepared to do immediate definitive surgery for the removal of the parathyroid tumor.

Summary and Conclusion

A case of primary hyperparathyroidism due to parathyroid adenoma is presented. The patient showed evidence of this disease on the skull film on her first admission in 1947. She had a clinical remission lasting almost six years. Preterminally the patient developed the rare complication of parathyroid hormone intoxication, precipitating coma and death. A review of the literature reveals only about 10 recorded cases of similar nature. The effects of parathyroid hormone in physiologic and excessive amounts are discussed, and the general systemic manifestations and the diverse and perplexing character of the disease are emphasized. In the presence of hyperparathyroidism, once the diagnosis is established or even suspected, only definitive surgery for the removal of the tumor of the parathyroid gland should be attempted.

Summario in Interlingua

Hyperparathyroidismo primari esseva diagnosticate rarmente ante morte usque Mandl in 1925 reportava su successo in le excision de un adenoma parathyroide in un patiente con osteitis fibrose cystic. Le studios subsequente de Albright e su collaboratores establiva hyperparathydroidismo firmemente como un ben-definite entitate clinic.

On crede generalmente que le incidentia de hyperparathyroidismo primari es multo basse. Le causa le plus commun—incontrate in circa 90 pro cento del casos—es un adenoma parathyroide. Le declaration es insidiose. Le morbo es chronic. Su remissiones varia in extension. Le diagnose precoce es indispensabile pro prevenir un compromisso permanente del renes, del ossos, e del systema cardiovascular. Le condition debe esser prendite in consideration in patientes con calculos urinari, benigne tumores ossee, o fracturas sin altere explication.

Hyperparathyroidismo, post suspicion de su presentia, es facilemente diagnosticate per medio de characteristic constatationes clinic, roentgenologic, e chimic. Tamen, in consequentia de su raritate e a causa del variabilitate de su manifestationes clinic, il occurre in le majoritate del casos reportate un infelice e a vices mortal perdita de tempore inter le declaration del symptomas e le establimento definitive del diagnose. Ab le puncto de vista biochimic le condition es typicamente characterisate per hypercalcemia, hypercalciuria, hypophosphatemia, e hyperphosphaturia. Quando le ossos es afficite, le valor seral de phosphatase alcalin es elevate.

Hyperparathyroidismo se manifesta in morbo del systema skeletic o del vias urinari o per le symptomas de hypercalcemia. Iste manifestationes es attribuibile al excessos del secretion de hormon parathyroide. In le majoritate del casos, le symptomas de hypercalcemia—i.e. debilitate muscular, hypotonia, nausea, anorexia, e constipation—ha un rolo plus tosto secundari. Tamen, de tempore a tempore il occurre un caso in que le elevation subitanee del calcium seral precipita un grave episodio de extreme disquietude, vomito intractabile, tachycardia, prostration, coma, e morte—un condition cognoscite como acute intoxication parathyroide, simile a illo observate in animales tractate con doses excessive de "parathormon." Iste complication, que es rar sed periculose, occurre usualmente quando le calcium del sero monta a un nivello plus alte que 17 mg per 100 ml.

Le caso hic presentate pertine a iste ultime gruppo, le gruppo del si-appellate acute intoxication parathyroide. Un revista del litteratura revela solmente circa 10 casos reportate. Le patiente esseva un femina de racia blanc de 25 annos de etate con hyperparathyroidismo primari como resultato de un adenoma parathyroide al polo inferior del lobo dextero-thyroide. Al tempore de su prime hospitalisation in 1947, signos del morbo esseva evidente in un roentgenogramma cranial. Sequeva un remission clinic de un duration de quasi sex annos. Le diagnose esseva establite ante morte e confirmate al necropsia. Le secunde (e ultime) hospitalisation del patiente occurreva in 1952. A iste tempore un roentgenogramma cranial revelava le perforation del integre domo per micre e grande lesiones osteolytic. Repetite studios monstrava le sequente valores: Calcium seral, 17,7 mg per cento ml; phosphoro, 2,9 mg; e phosphatase alcalin, 25,7. Le glandulas submaxillari se habeva allargate grandemente e esseva de un consistentia multo firme. Le curso del patiente se deteriorava rapidamente. Ante le termino illa disveloppava le complication rar de acute intoxication per hormon parathyroide. Isto precipitava coma e morte. Le morte occurreva post le effectuation de un biopsia de glandula submaxillari, lo que debe esser considerate como un manovra innocente.

Le effectos de hormon parathyroide in quantitates physiologic e excessive es discutite. Le manifestationes systemic general e le natura multiforme e confundente del morbo es signalate. Es concludite que in le presentia de hyperparathyroidismo le sol operation permissibile es le excision del tumor parathyroide. Omne altere manovra chirurgic pote precipitar un acute crise parathyroide.

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STEATORRHEA WITH DIABETES: A CASE REPORT *

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THE diabetic, like any other patient, may develop various types of diarrheal diseases unconnected with his diabetic state. Several types of diarrhea have, however, been reported as associated with the diabetic state. What Bargen et al.[3] and other authors have termed "the diarrhea of diabetes" is a watery, nonfatty, nocturnal diarrhea of unknown etiology. Bargen also referred to steatorrhea in diabetics due to pancreatic insufficiency. More recently, Berge [4] has reported a third variety of diarrhea in diabetes. He described six patients in whom steatorrhea was associated with diabetes and neuropathy, and two more in whom it was associated with diabetes without clinical evidence of neuropathy. In the discussion of that paper, Adlersberg described a similar patient who responded dramatically to cortisone, but he made no statement concerning neuropathy in that patient. This report adds another patient with diabetes and steatorrhea without evidence of pancreatic insufficiency.

CASE REPORT

A 57 year old white male was admitted to the hospital September 20, 1955, because of severe weakness for two weeks, and diarrhea and weight loss for two years. He had had severe diabetes for 35 years which had required repeated admissions to this and other hospitals for the treatment of acidosis and hypoglycemia, and had required as much as 120 units of insulin daily. He recalled having had an episode of diarrhea in childhood. His weight on previous admissions had varied between 130 and 140 pounds. He complained of a 20 pound weight loss in the last two years, associated with eight to 10 copious, foul-smelling stools daily. He had been hospitalized elsewhere for six months in 1955 for the treatment of arteriosclerosis obliterans and osteomyelitis of the toes of the left foot. Two weeks before admission he had suffered a stroke involving his left side. Because of continued weakness he was admitted to the hospital.

Physical Examination: Patient was an emaciated, dehydrated white male lying on his back, appearing severely and chronically ill. Height 5 ft. 8 inches; weight, 90 pounds; pulse, 72; blood pressure, 120/60 mm. of Hg; temperature, 98.0° F. Fundi showed retinal arteriosclerosis; the tongue was smooth around the edges, and there was moderate cheilosis. The abdomen was protuberant, with no palpable masses and no tenderness. There were no abnormalities of the rectum or genitalia. There was weakness of the left arm and leg, and left central facial weakness. Babinski's sign was present on the left; deep tendon reflexes were absent in all limbs; vibratory sense was present throughout. There was no postural hypotension. Pulses were barely palpable in both feet, and the feet were cool.

Laboratory Examinations: On admission the hemoglobin was 12.4 gm.; white blood cell count, 10,300, with a normal differential. In the urine, sugar was 4 plus; albumin, a trace; acetone, 1 plus. Serum potassium was 2.2 mEq./L.; sodium, 150

* Received for publication October 19, 1956.
Approved for publication by the Committee on Research and Publication, Veterans Administration Center, Los Angeles.
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mEq./L.; chlorides, 91 mEq./L.; calcium, 9.0 mg.%; A/G ratio, 3.9/2.1; blood sugar 400 mg.%; prothrombin time, 100%. X-ray examination of the chest was normal An upper gastrointestinal x-ray series revealed a duodenal ulcer; a small bowel series showed a "deficiency pattern"; the barium study of the colon was normal. Repeated stool examinations were negative for ova and parasites.

Hospital Course: The fluid and electrolyte abnormalities were corrected by appropriate intravenous fluids. The patient gradually regained his strength and appetite, but the frequent foul-smelling stools continued. Insulin requirement was 20 units of NPH insulin daily.

Special Studies: The stools were grossly soft, tan and occasionally semiliquid. Microscopically there was a marked increase in fat and fatty acid crystals, with few meat fibers. On a measured diet (Wollaeger,[9] 1946) containing 102 gm. of fat daily, the fat excretion was abnormally high, totaling 23 gm. daily during one three-day period, and 46 gm. daily during another (normal, less than 7 gm.), while nitrogen excretion was in the normal range (3.26 gm. daily). Aspiration of the stomach for one hour produced 68 c.c., containing 4.2 mEq. of hydrochloric acid. Duodenal secretion was 8 c.c. in 15 minutes; bicarbonate content was 75 mg./c.c. After secretin was administered the volume rose to 20 c.c./15 min., and bicarbonate to 87 mg./100 c.c. Seventy-seven thousand five hundred units of amylase were found in 100 c.c. of duodenal secretion. In the spinal fluid, protein was 90 mg.%; there were no cells or other abnormalities.

Further Treatment: Crude liver extract was injected intramuscularly daily, vitamins were given orally and parenterally, and folic acid and pancreatin were administered. After six months there was no effect on the stool volume or the patient's weight. Prednisone was then begun, in dosage of 15 mg. daily, along with vigorous antacid therapy. There was gradual improvement in the diarrhea and a gain in weight. After six months of treatment the patient had gained 27 pounds, was having two formed stools daily, was taking 80 units of insulin daily and was feeling well.

Comment

Diabetic diarrhea has been noted in previous reports as being watery, not fatty.[7, 8] Reports of large numbers of patients with sprue [1, 6] contained no patients with diabetes; in fact, Bodansky [5] refers to the flat glucose tolerance curve and hypochlorhydria as distinguishing features of idiopathic steatorrhea. In the cases of steatorrhea with diabetes reported by Berge,[4] the diabetes was severe and long-standing, as in this case; his case 5 also had a duodenal ulcer. The role of neuropathy in this patient is somewhat obscured by the recent stroke causing hemiparesis, and perhaps accounting for the elevated spinal fluid protein; postural hypotension was absent, vibratory sense was present, but the complete absence of deep tendon reflexes would seem to support the diagnosis of diffuse neuropathy.

Summary

Steatorrhea developed in a man with long-standing, severe diabetes which did not appear to have the other findings of sprue, nor did it respond to liver or vitamin treatment. No other cause for the steatorrhea could be found, and the tests of pancreatic function were normal. Evidence for diabetic neuropathy was equivocal. Treatment with prednisone resulted in remission of the steatorrhea and a 27 pound weight gain.

SUMMARIO IN INTERLINGUA

Un masculo de racia blanc de 57 annos de etate esseva hospitalisate le 20 de septembre 1955 a causa de sever grados de debilitate de un duration de duo septimanas e diarrhea con perdita de peso de un duration de duo annos. Diabete labile de grados sever habeva essite presente depost 35 annos. Sever arteriosclerose oblitterante habeva quasi resultate in le perdita del pede sinistre. Hemiparese sinistre habeva occurrite duo septimanas ante le hospitalisation. Le peso usual del patiente esseva 130 libras (de 453 g). Ille habeva perdite 40 libras, 20 in le curso del passate duo annos. Ille esseva grave- e chronicamente malade. Esseva constatate cheilosis, hemiparese sinistre, un positive signo de Babinski al latere sinistre, sed le absentia complete de reflexos de tendine profunde a ambe lateres. Le hemoglobina esseva 12,4 g. Urinanalyse: Sucro, 4 plus; albumina, tracia; acetona, 1 plus. Albumina, 3,9 g; globulina, 2,1 g. Roentgenogrammas gastrointestinal monstrava un ulcere duodenal, un configuration de carentia in le intestino tenue, e un colon normal. Le patiente recipeva fluido intravenose e therapia supportative. Su fortias e su appetito se meliorava. Le frequentia e le character del evacuation non cambiava. Le excretion diurne de grassia amontava a inter 23 e 46 g, con un dieta continente 102 g de grassia per die. Le excretion de nitrogeno esseva normal. Le production de acido per le stomacho esseva intense. Le secretion de enzymas e le responsa bicarbonatic del pancreas a secretina esseva normal. Sex menses de tractamento con injectiones de crude extractos hepatic e vitaminas e le administration oral de acido folic a pancreatina remaneva inefficace. Un curso de sex menses de prednisona reduceva le evacuationes al production de feces formate duo vices per die. Le patiente ganiava 27 libras.

Durante que diarrhea aquose ha longemente essite associate con diabete, Berge ha recentemente describite plure casos de steatorrhea con sever grados de diabete de longe duration, usualmente in association con neuropathia. Le caso hic reportate es apparentemente del mesme genere. In illo le responsa a prednisona esseva incoragiante.

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HEPATIC HYDROTHORAX *

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Pleural effusion may present itself either as the herald or as the accompaniment of significant disease, with the frequency of its occurrence depending upon the nature and the site of the disease. Usually, the effusion is the result of cardiac failure or of inflammatory or neoplastic conditions involving the pleura, lung or mediastinum. At times it is seen in association with tumors of the female pelvic organs and ascites (Meigs' syndrome).[1] Only occasionally has pleural effusion been attributed to cirrhosis of the liver.[2, 3] That its occurrence is only occasional in this disease is confirmed by the statistics of our hospital. A review of these figures from the opening of this institution in November, 1950, until May, 1956, showed that, of the approximately 250 cases of cirrhosis admitted during this period of more than five years, only one had chest fluid that could be attributed to the hepatic disease. This is an incidence of approximately 0.4%.

Since the pleural effusion in cirrhosis of the liver has been found to be a transudate, not an exudate,[2, 3, 4, 5] we have given this article the title of "Hepatic Hydrothorax" in order to acknowledge and to stress this relationship.

Though the first description of pleural effusion in cirrhosis is ascribed to Laennec, such cases have been infrequently recorded in the literature. It is this dearth of chronicled reports that led us to record the following case of hepatic hydrothorax, diagnosed as such on a clinical basis. In addition, our intent is to give particular consideration to the mechanisms of production of the effusion and the diagnostic features serving to identify it as "hepatic."

Case Report

The patient, a 63 year old white male laborer, was admitted to this hospital on February 19, 1952. As he spoke English poorly, a satisfactory history was not obtained. However, it was learned from a member of his family that he had been a heavy gin drinker for many years, and that for a few months preceding his admission he had noted pains in and swelling of the abdomen and lower extremities. Physical examination on admission revealed an elderly white male who appeared chronically ill. His temperature was 98° F., with the pulse regular in force and rhythm at the rate of 94, and a blood pressure of 90/60 mm. of Hg. The neck veins were not distended, and the lungs and heart were normal. The abdominal examination disclosed evidence of ascites, with the lower border of the liver firm and just barely palpable; the spleen was not felt. There was marked edema of the feet and ankles. The remainder of the physical examination was not remarkable. The urine showed a specific gravity of 1.022, with 3 to 5 white blood cells per high power field; the blood Kahn was negative; the complete blood count was normal except for a red blood cell count of 3.45 million and hemoglobin of 9.6 gm.; the blood urea nitrogen was normal; the serum albumin and globulin were 1.6 gm. and 4.3 gm., respectively;

* Received for publication December 14, 1956.

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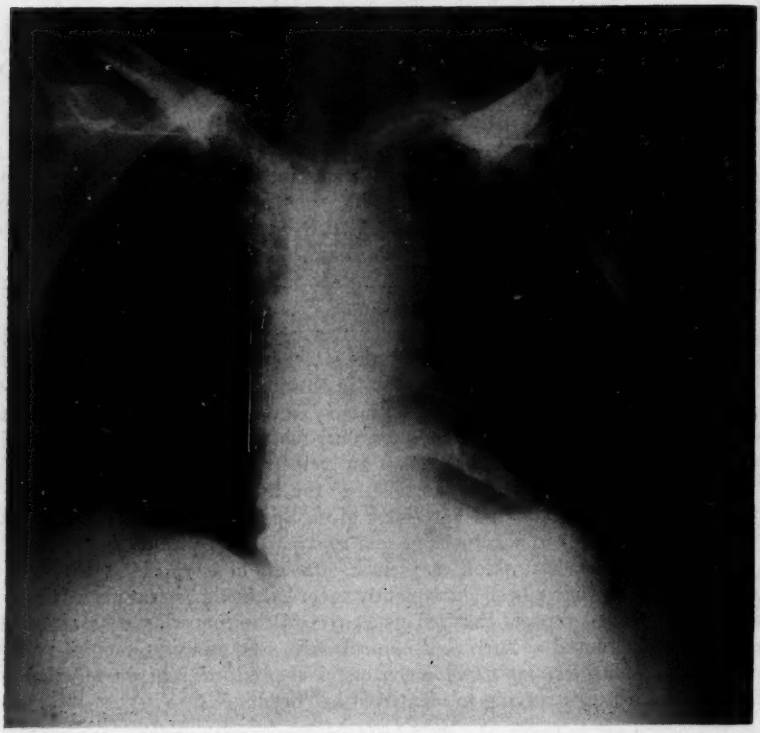

FIG. 1. Posteroanterior chest roentgenogram showing elevation of the leaves of the diaphragm due to ascites (February 19, 1952).

thymol turbidity, 12 units; cephalin flocculation, 4 plus at the end of 48 hours; total serum bilirubin, 1.2 mg.; prothrombin time, 17 seconds, with a control of 14 seconds. An x-ray of the chest on February 19, 1952 (figure 1), showed elevation of both leaves of the diaphragm due to the ascitic fluid. An esophagram, a gastrointestinal series and a barium enema were normal. An electrocardiogram was normal.

During the major part of his hospital stay the patient was treated as a decompensated case of cirrhosis of the liver with a high protein, high carbohydrate, low fat and low sodium diet; multivitamins, including vitamin K; crude liver extract, and mercurial diuretics. After transudation of the pleural fluid had occurred, four transfusions, each consisting of 250 c.c. of blood, were given on different days in March, for therapy of the anemia.

On the sixth day of hospitalization (February 25, 1952) he became markedly dyspneic. X-ray of the chest on this day (figure 2) showed a massive pleural effusion on the right. A thoracentesis easily yielded 1,900 c.c. of clear amber fluid. Subsequently, because of recurrence of the dyspnea due to further transudation of fluid, thoracentesis on the right was repeated approximately once weekly during the next three months, with the last tap on May 19, 1952. The total amount of fluid removed by the chest taps, which numbered 13 in all, was approximately 25,000 c.c. Several examinations of the fluid showed it to have the characteristics of a transudate,

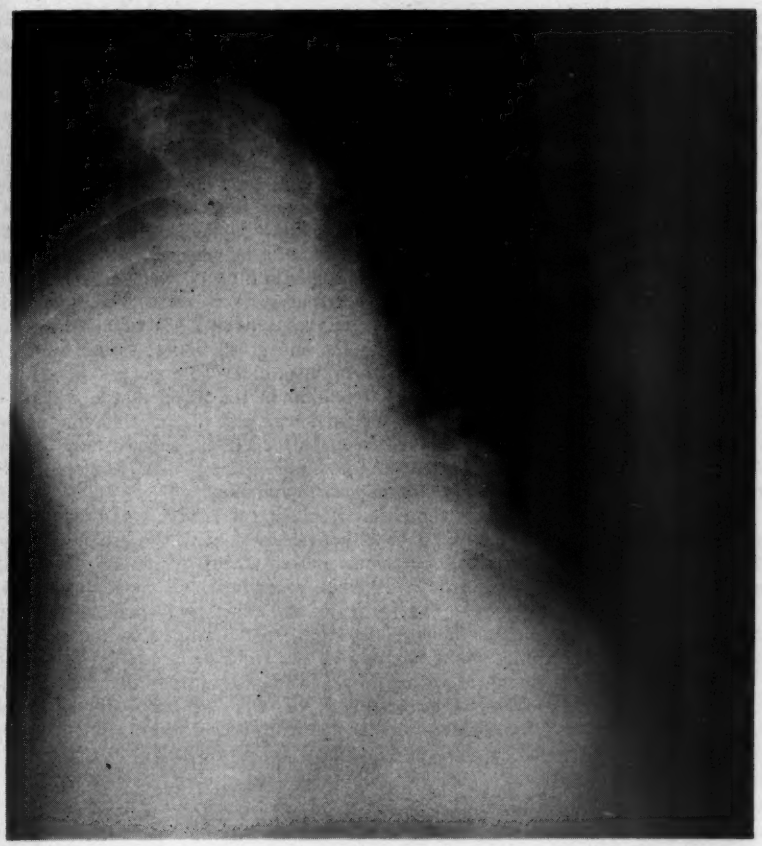

FIG. 2. Posteroanterior chest roentgenogram showing the massive hydrothorax on the right without cardiac displacement or evident enlargement (February 25, 1952).

with specific gravities varying between 1.008 and 1.012, and protein content of approximately 0.5%; the fluid contained no malignant cells. After the fluid appeared, circulation time and venous pressure determinations were done on several occasions in February and March. The circulation times were practically within normal limits, but the venous pressures were found to be slightly elevated, varying between 14 and 17 cm. Therapy for cardiac failure was empirically instituted on March 1, 1952, when dyspnea was again pronounced, owing to the re-accumulation of pleural fluid. The patient, already on a low sodium diet, was digitalized and maintained on digitalis until March 21, 1952, when it was discontinued as being ineffective in preventing the formation of pleural fluid. Cardiac failure was thought, therefore, not to be responsible for the hydrothorax; in addition, this diagnosis was discarded for lack of other clinical evidence. Even the frequent administration of mercurial diuretics failed to prevent the accumulation of fluid. Electrocardiograms during this period were not remarkable except for evidence of digitalis effect. On April 24,

1952, the patient developed a supraventricular tachycardia of approximately 150. Though 1,900 c.c. of pleural fluid were removed and carotid sinus pressure on each side separately was applied, the tachycardia failed to subside. However, after the administration of 0.8 mg. of lanatoside C intravenously, the cardiac arrhythmia disappeared in approximately one hour. Subsequently he did not have a recurrence of the arrhythmia, nor did he receive any more digitalis. With continuation of the low sodium diet, crude liver extract and vitamins, the patient's condition gradually improved. Thoracenteses were done, as noted above, only until May, 1952; after this date, with the fluid receding, no further chest taps were necessary. Just prior to his discharge in July, 1952, the red blood cell count and the hemoglobin were 4.0 million and 12.2 gm., respectively. The liver function tests, which for several months after admission had demonstrated persistent abnormalities of the serum albumin and globulin, thymol turbidity and cephalin flocculation tests, were as follows: (1) serum albumin and globulin, 3.6 gm. and 3.4 gm., respectively; (2) thymol turbidity, 5.0 units; (3) cephalin flocculation 3 plus at the end of 48 hours; serum bilirubin, 0.5 mg.; (4) intravenous administration of bromsulfalein (5 mg. per kilogram), performed for the first and only time, 5% retention in the blood at the end of 45 minutes. By this time the edema of the feet and legs had disappeared, the ascites was not detectable, and an x-ray of the chest on July 22, 1952, showed only a small amount of pleural fluid in the right costophrenic sinus. The patient was discharged from the hospital on July 29, 1952, practically asymptomatic.

Examined after discharge from the hospital on August 12, 1952, and on October 13, 1952, the patient had no complaints on either occasion, with the ascites still not discernible. The hemograms on both occasions showed normal white and differential counts, with the red blood cell and hemoglobin determinations approximately 4.0 million and 11.5 gm., respectively. The x-rays of the chest on these dates revealed a further decrease in the pleural fluid on the right, to the point that the x-ray on October 13, 1952, showed only slight blunting of the right costophrenic sinus, with the leaves of the diaphragm lower owing to the disappearance of the ascitic fluid. The serum albumin and globulin on August 12, 1952, were 3.5 and 3.0 gm., respectively. Recently, an inquiry concerning the patient's subsequent clinical course elicited the information that he had died at home in August, 1953, of a cerebral hemorrhage. No autopsy was done.

Comment

As the patient, a male, showed no evidence of disease of any of the organs of the chest cavity, it was believed that the pleural fluid having the characteristics of a transudate was associated with the underlying cirrhosis of the liver. However, since the transudative fluid gave rise to dyspnea, the diagnosis of cardiac failure was at one time considered and acted upon. However, it was soon discarded as the formation of chest fluid was not influenced by digitalis or other therapy directed towards cardiac failure. The slight elevation of the venous pressure was attributed to the pressure of the pleural fluid on the mediastinum, since it is known that a hydrothorax can provoke this elevation.[6] The paroxysmal cardiac arrhythmia was thought to have been precipitated by the hydrothorax. Attention is drawn to the fact that, with the return of the serum albumin to a fairly normal level, both the pleural and ascitic fluids disappeared.

Discussion

The frequency of pleural fluid in association with cirrhosis of the liver or hepatic hydrothorax has been variously noted. Vedel and Puech [7] reported an

incidence of approximately 8 to 9%, but a number of their cases showed effusions which could be attributed to causes other than cirrhosis. Bockus [8] states that routine study by x-ray will show the presence of fluid in the pleural cavities of 10% of patients who have advanced cirrhosis. McKay et al.[2] described six cases of "hepatic" pleural fluid out of approximately 600 cases of cirrhosis of the liver, an incidence of approximately 1%. Tinney and Olsen,[3] in a study of the causative factors of pleural effusion, listed eight cases with pleural fluid out of 274 cases of cirrhosis of the liver, an incidence of approximately 3%. As previously mentioned, our own incidence is approximately 0.4%. It can be seen that, superficially, there is a discrepancy between, on the one hand, our incidence and those of McKay et al. and of Tinney and Olsen and, on the other hand, that of Bockus. This discrepancy is only apparent and not real, since Bockus reported the incidence of hepatic hydrothorax in terms of the advanced cases of cirrhosis, while we and the others estimated it on the basis of all cases of cirrhosis, not only those in the advanced stage.

"Hepatic" fluid seems to have no predilection for one or the other pleural space. Ingelfinger [9] states that fluid may occasionally appear in both pleural cavities, particularly the right. McKay et al.[2] reported six cases, one with fluid on the right, two with fluid on the left and three with fluid bilaterally. Christian [5] reported a case with fluid on the left, while Frothingham [4] had one with fluid on the right and Schalm at al.[10] another with fluid on this side. Our own patient had fluid on the right.

There appears to be mellifluous agreement concerning the nature of the "hepatic" fluid in the chest. McKay et al., Tinney and Olsen, Frothingham and Christian all reported cases of cirrhosis with the pleural fluid showing the characteristics of a transudate; our patient also had a hydrothorax. However, in Christian's case and two of the eight cases listed by Tinney and Olsen, the fluid was also hemorrhagic. No explanation for the presence of blood in these fluids was given.

The "hepatic" chest fluid in patients with cirrhosis is usually abundant. According to McKay at al. small effusions of less than 500 c.c. denote, as a rule, disease other than cirrhosis. Their cases, and those of Christian, Schalm et al., and our own case, all had large amounts of pleural fluid. Frothingham's case deserves special comment—approximately 467,000 c.c. of fluid were removed from the right pleural cavity!

It seems that the hepatic hydrothorax is manifest only when the cirrhosis is associated with hypoalbuminemia and ascites. The case reported by Frothingham, the one described by Christian, that mentioned by Schalm et al., the cases reported by McKay et al. and our own—all had hypoalbuminemia and ascites in association with the pleural fluid. From these cases it may be gathered that the association between the pleural fluid on the one hand, and the hypoalbuminemia and ascites on the other hand, is based on the following relationship: that the hepatic hydrothorax does not precede, in appearance, the hypoalbuminemia and ascites, but either occurs simultaneously with or follows their appearance. In none of these cases was a cause for the pleural effusion other than cirrhosis found. It would seem that if pleural fluid is found in a patient with cirrhosis who does not show hypoalbuminemia and ascites, another cause for the pleural fluid should be searched for. It may well be that, since ascites is related to the presence of hypoalbuminemia, which lowers the osmotic

pressure of the blood, the common denominator in all these cases is low serum albumin.

As noted, hypoalbuminemia and ascites either occur simultaneously with or precede the appearance of the "hepatic" pleural fluid. If they occur before the appearance of the pleural fluid, either one or both presumably participate in its production; if they occur simultaneously with the pleural fluid, the same conclusion is still a possibility. To appreciate their roles, one should consider at least briefly the causes of transudative fluid in patients with cirrhosis of the liver. According to Ingelfinger,[9] such transudation is the result of the combined influences of systemic and local factors, with local factors determining the site of transudation. In the development of ascites, for example, at least two systemic factors and one local factor [9] are essential. The two systemic factors are (1) hypoalbuminemia, and (2) water retention, possibly resulting from the inability or decreased ability of the liver to destroy not only the antidiuretic principle of the posterior pituitary but also VDEM or ferritin, another antidiuretic agent (which is also vasodepressor) formed in muscle and the liver itself, while the local factor is portal hypertension. In the patient with hepatic hydrothorax, who, as noted, also has ascites, the same well known systemic and local factors are present as in one with ascites only, but the local factors responsible for the pleural fluid appear to be obscure. However, despite their obscurity, it may be possible to espy their hazy outlines.

There appear to be at least three local factors, each capable of giving rise to a hepatic hydrothorax when combined with the local and systemic causative factors of ascites. Described as a possible mechanism for the production of "hepatic" pleural fluid is an increase in the pressure of the azygos vein subsequent to the formation of collaterals between this system of veins and that of the portal vein.[11] This may be regarded as the first local factor. For the sake of brevity in referring to this factor, the increase in pressure in the azygos vein may be termed "azygos hypertension," just as an increase in pressure in the portal vein is alluded to as "portal hypertension." Another factor may be gleaned from the studies of Meigs et al.[12] Calling attention to the association of hydrothorax and ascites with certain large ovarian tumors (a syndrome which has been extended to include other pelvic tumors), they incriminated the ascitic fluid itself by demonstrating, after an intraperitoneal injection of India ink, the movement of fluid through the diaphragmatic lymphatics from the peritoneal cavity into a pleural cavity. This translymphatic movement of ascitic fluid can be considered to be the second local factor. Still a third local factor, also incriminating the ascitic fluid, seems to be a possibility. With the opening of a direct channel between the peritoneal and pleural cavities, this factor is born. This channel between the two cavities may be tunneled along two different routes. First, it has been shown that congenital defects exist in the musculature of the diaphragm,[13] and that increased pressure within the peritoneal cavity will rupture the pleuroperitoneal membrane overlying such a defect, as by air in cases of therapeutic pneumoperitoneum which develop an unexpected pneumothorax.[14] Second, it has been postulated that air under pressure in the peritoneal cavity may rupture the peritoneum overlying the retroperitoneal tissues and dissect its way into the mediastinum,[15] and from the mediastinum air may rupture through the pleura and thus produce a pneumothorax.[16] In support of the retroperitoneal

pathway is the presence of air in the retroperitoneal space on the right of a recently hospitalized patient with pulmonary tuberculosis who was under treatment with pneumoperitoneum (figure 3). However, an x-ray of the chest showed that the air had not traveled as far as the mediastinum. Attention was directed to the right retroperitoneal area, as the patient had complained of pain in this region soon after air had been administered intraperitoneally. In similar fashion, it is not unlikely that ascitic fluid under pressure may produce one or the other communication between the peritoneal and pleural cavities through which the fluid may flow. The validity of this hypothesis may be tested by two procedures: (1) a pneumoperitoneum can be induced to note whether a hydropneumothorax develops on the side of the hydrothorax, and (2) as much ascitic fluid as possible can be removed, if therapeutically advisable, to see whether the amount of pleural fluid decreases. It can be readily seen that with these maneuvers a hydropneumothorax and a decrease in the amount of pleural fluid should develop relatively rapidly if a diaphragmatic channel is present, and only slowly

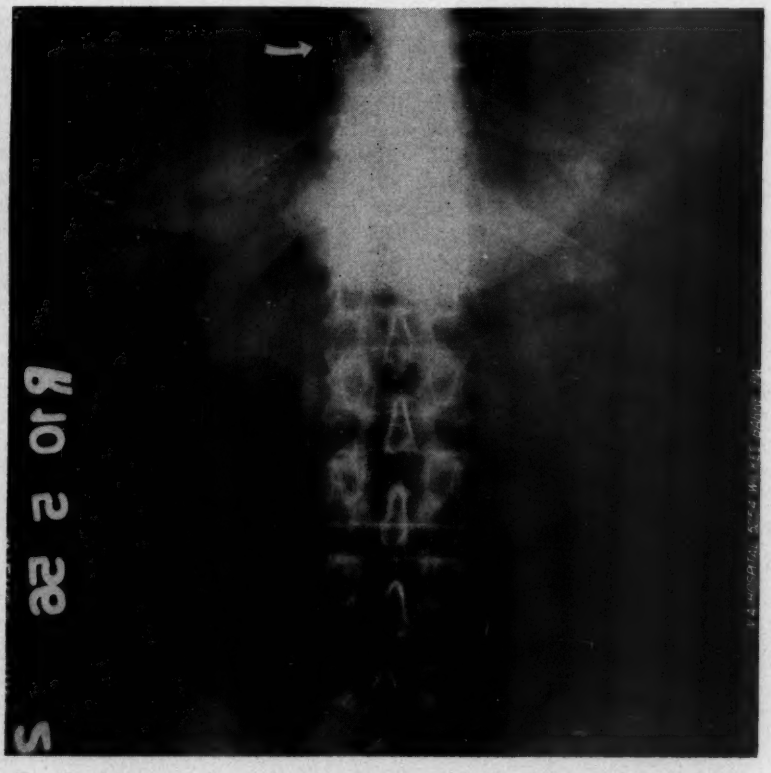

FIG. 3. Anteroposterior supine roentgenogram of the abdomen showing air in the retroperitoneal space on the right, following pneumoperitoneum in a patient with tuberculosis.

if the communication between the peritoneal and pleural cavities is through the retroperitoneal tissues and the mediastinum. Anticlimactically, in Meigs' syndrome both of these methods have been tried but have failed to demonstrate a pleuroperitoneal communication.[17]

Not having given serious consideration to the pathogenesis of the pleural fluid at the time the patient was in the hospital, we did not attempt to ascertain which one of the local factors was exerting its influence, although all three appear susceptible to determination. The methods for the diagnosis of a pleuroperitoneal communication have been described. Azygos hypertension may be inferred if the azygos vein can be shown to be distended, and this distention can be found by x-ray examination of the chest.[18, 19] Intraperitoneal injection of a dye with its subsequent recovery in pleural fluid within a relatively short time would point, in the absence of a pleuroperitoneal channel, to the movement of ascitic fluid through the lymphatics of the diaphragm.

It can be inferred that, if the ascitic fluid is the responsible factor, as in Meigs' hypothesis or as in the pleuroperitoneal communication theory, the pleural fluid would probably appear after the ascites. However, if azygos hypertension, which is secondary to portal hypertension, is responsible, the occurrence of hypoalbuminemia would probably cause the simultaneous transudation of both pleural and ascitic fluids. This is true only if the azygos hypertension is present at the time the low serum protein develops; if the azygos hypertension occurs after the hypoalbuminemia becomes manifest, the pleural fluid will occur after the ascites.

It would appear that no single local factor is applicable to all cases of hepatic hydrothorax. Hemorrhagic chest fluid is probably best explained on the basis that bleeding occurs with the traumatic formation of one or the other pleuroperitoneal communication, if a clotting defect of the blood due to liver disease itself is excluded. If a clotting defect is present, then hemorrhagic chest fluid may appear as a result of any one of the local factors. The unilateral hydrothorax free of blood may also be accounted for by any of the local factors. However, the bilateral hydrothorax appears to eliminate almost completely the hypothesis of pleuroperitoneal communications. Though the bilateral effusion may be the result of perforation either of bilateral defects in the diaphragm or of both pleural membranes via the mediastinum, it is realized that this conception attempts to stretch the imagination further than reason will permit. It may well be, then, that the factor responsible for this phenomenon is either one of the other two, i.e., Meigs' explanation, or azygos hypertension. It appears safe to state that in cirrhosis of the liver the ascitic fluid will disappear with correction of the low serum albumin, even though the portal venous pressure remains elevated.[9] The pleural fluid will probably also disappear with return of the serum albumin to a normal level, whatever the local factor pertaining to the development of the fluid. It should be added that correction of the low serum albumin may indicate an improvement in liver function to the point that the antidiuretic agents are normally metabolized; this of course, also favors the disappearance of the ascitic and pleural fluids. In any event, both the ascitic and the pleural fluids in the reported case disappeared when the serum albumin became normal.

The therapy of hepatic hydrothorax should be directed to the underlying cirrhosis of the liver, with thoracentesis indicated for the relief of dyspnea.

However, the knowledge, if it can be obtained, that there exists a communication between the pleural and the peritoneal cavities might be of therapeutic benefit, since the removal of ascitic fluid in sufficient quantity from the abdomen rather than from the chest would bring about more prolonged relief of dyspnea. The prognosis of a patient with a hepatic hydrothorax is chiefly dependent upon the underlying cirrhosis, which is in a decompensated stage.

Before the diagnosis of hepatic hydrothorax is made, other causes of pleural effusion must be excluded, particularly disease of the organs within the chest cavity and, in a female patient, a tumor of the pelvic organs. In addition, if the pleural fluid is to be attributed to cirrhosis of the liver, both ascites and hypoalbuminemia should be present. Furthermore, the pleural fluid should be large in amount and have the characteristics of a transudate, namely a low specific gravity and a low protein content. It is believed that the case reported satisfied these criteria.

Summary

1. Of approximately 250 cases of cirrhosis of the liver seen at this hospital in a period of more than five years, only the one reported had pleural fluid that was attributed, on a clinical basis, to the hepatic disease. The incidence of hepatic hydrothorax in this series of cases was approximately 0.4%, an incidence that reflects the infrequency of its occurrence noted in other studies. In the reported case the transudative pleural fluid and the ascites disappeared when the hypoalbuminemia was corrected.

2. The diagnosis of hepatic hydrothorax should be based on the following: (a) the absence of any disease other than cirrhosis of the liver that could cause a hydrothorax, (b) the presence of both ascites and hypoalbuminemia, and (c) the formation of abundant amounts of pleural fluid having the characteristics of a transudate.

3. The transudation of "hepatic" pleural fluid in cirrhosis of the liver appears to be dependent upon the combined influence of three causative factors, two systemic and one local, that produce ascites, and any one of three local causative factors responsible for the pleural fluid. The three factors responsible for the ascites are: (a) hypoalbuminemia, (b) water retention due to the inability of the liver to metabolize the antidiuretic agents normally found in the body, and (c) portal hypertension. The three local factors responsible for the pleural fluid, whose presence appears susceptible to ascertainment, are: (a) azygos hypertension, (b) Meigs' hypothesis of movement through the diaphragmatic lymphatics of ascitic fluid into a pleural cavity, and (c) communications between the peritoneal and pleural cavities through rupture by ascitic fluid either of the pleuroperitoneal membrane overlying a congenital defect of the diaphragm, or of the peritoneum overlying the retroperitoneal space, with subsequent dissection of the fluid into a pleural cavity.

4. It would seem that, whatever the local factor, correction of the hypoalbuminemia along with the presumable correction of the associated disturbance in metabolism of the antidiuretic agents should lead to the disappearance of the pleural fluid.

5. It would appear that no single local factor is responsible for all cases of hepatic hydrothorax. The hemorrhagic hydrothorax seems to be best explained on

the basis that bleeding occurs with the traumatic production of one or the other pleuroperitoneal communication. The unilateral hydrothorax may be due to any one of the three local factors. The bilateral hydrothorax is probably best accounted for by Meigs' hypothesis or by azygos hypertension.

SUMMARIO IN INTERLINGUA

Le disveloppamento de un effusion pleural que pote esser attribuite a cirrhosis del hepate es relativemente rar. Un tal caso esseva trovate in un revista de 250 casos de cirrhosis hepatic. Le termino "hydrothorace hepatic" es justificate proque in tal casos le fluido ha le characteristicas de un transsudato.

Un caso typic es reportate in detalio. Ascites esseva presente coincidentemente. Marcate grados de hypoalbuminemia (1,6 g) esseva etiam presente. Le effusion requireva repetite thoracocenteses, con le elimination de un total de 25.000 cm^3 de fluido ab le thorace dextere.

Es presentate un revista del litteratura pertinente. Es accentuate le factores que es interessate in le formation del hydrothorace, i.e. hypoalbuminemia, retention de aqua, augmento del pression in le venas azygotic, e le migration possibile de fluido ascitic a in le cavitate pleural via le canales lymphatic o altere.

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SUCCESSFUL TREATMENT OF RECURRENT URIC ACID RENAL CALCULI WITH PROBENECID (BENEMID) *

By Arthur Bernstein, M.D., F.A.C.P., David Bronsky, M.D., and Alvin Dubin, M.S., *Chicago, Illinois*

Uric acid stones comprise 4 to 6% [1, 2] of all renal calculus disease. Treatment by surgical and dietary measures, by alkalinization of the urine and with salicylates has not been satisfactory. Such stones occur frequently in patients with gout. Probenecid (Benemid), a potent uricosuric agent, may effect a reversal of the clinical course of gout.[3, 4] That it may also be highly effective in the treatment of recurrent uric acid stones in patients without symptomatic gout can be inferred by a consideration of the following case history.

Case Report

A 64 year old white man was observed on January 2, 1954, complaining of recurrent kidney stones of 18 years' duration. He stated that he had been in good health until the age of 46 years, when he experienced left lumbar pain with lancinating radiation to the groin. After 48 hours the pain subsided, and upon micturition he passed a dark brown, pinhead-sized calculus. Six months later he observed a second stone, and subsequently he continued to pass similar stones at the rate of one to three a month. Three years before the stones had become noticeably larger and more difficult to pass. Whereas previously they seldom exceeded the size of a pea, they now were often one quarter of an inch in diameter and frequently star-shaped. Occasionally they would lodge in the urethra and have to be "milked" out or extracted through the meatus with a forceps. Hematuria sometimes accompanied the passage of these large stones. One year before he had begun to pass "gravel," i.e., 20 or more pinhead- to pea-sized stones during one micturition. These occurred on the average of once or twice a month. At the same time the frequency of passage of large stones fell slightly. As at the onset, each passage of a stone or gravel was preceded by 48 to 72 hours of either right or left lumbar pain with radiation to the groin. They were unaccompanied by chills or fever. The patient denied ever

* Received for publication January 7, 1957.
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having had joint pain, and there was no familial history of renal calculi or gout. Throughout his illness he sought medical advice frequently. Therapeutic trials of low purine diets, alkalinization of the urine, forced fluid intake and use of salicylates were consistently ineffective. In time he became inured to pain and seldom required analgesics.

On physical examination the patient was a tall, very obese white man. He weighed 290 pounds. The blood pressure was 154/120 mm. mercury. Pulse, respiration and temperature were normal. Examination of the head, heart, lungs, abdomen and extremities revealed no abnormalities. The kidneys were not palpable, and there was no costovertebral angle tenderness. There were no tophi or joint deformities.

Laboratory examination revealed a hemoglobin of 84%. Urinalysis showed a trace of albumin and an occasional white cell upon microscopic examination. Chemical analysis of the calculi revealed them to consist of pure uric acid crystals. The blood nonprotein nitrogen was normal. The blood uric acid was 8.3 mg. per 100 c.c. An intravenous pyelogram revealed normal-appearing kidneys, ureters and bladder. Calculi were not visualized.

Management and Course (figure 1): The patient was placed on Benemid, 1.5 gm. daily, and a low calorie diet. An immediate effect was observed. The passage of large stones stopped at once. The gravel turned to "sand," i.e., occasional passage of approximately one quarter of a teaspoonful of minute stones. The sand appeared intermittently at less frequent intervals for 29 months and then stopped altogether. The small single stones also became less frequent, and after 29 months stopped appearing. The patient has passed no stones of any type now for five months. The distressing episodes of lumbar pain have been relieved. He has lost 30 pounds and his blood pressure is now within normal limits. The urine continues to contain a trace of albumin.

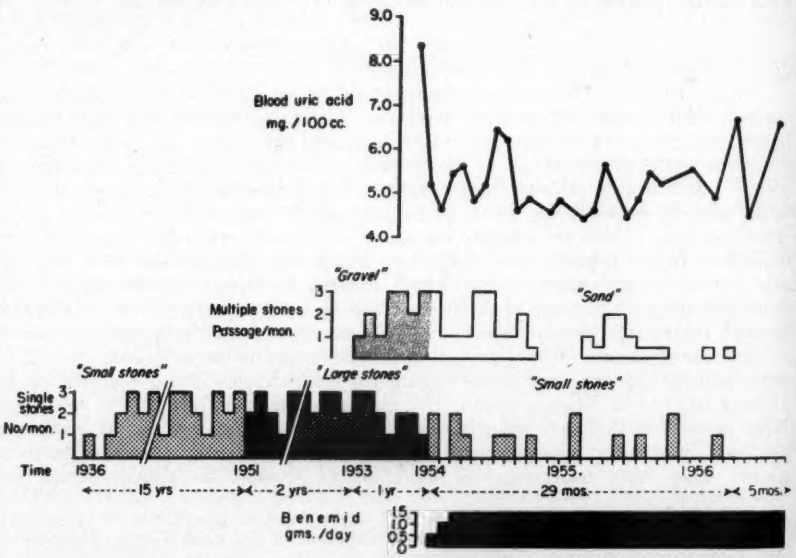

FIG. 1. Semischematic representation of passage of renal calculi for 18 years before and 34 months after onset of Benemid therapy. For explanation of terms see text.

Discussion

The mechanism of formation of uric acid calculi is not clearly understood. An increase in the formation of uric acid is undoubtedly an important factor. Such is the case in rare instances of obstructive uropathy due to uric acid stones following radiation or chemotherapy for leukemia.[5, 6] Here the apparent sequence of events consists of massive white blood cell destruction, liberation of enormous amounts of nucleoproteins, excessive production of uric acid, an increase in the size of the metabolic pool of uric acid with hyperuricemia, concentration in the kidney exceeding the solubility of urate in the urine, and precipitation of uric acid crystals blocking tubules and ureters.

Clinically, uric acid stones are observed frequently in patients with gouty arthritis. The reported incidence varies from 6 to 17%.[7, 8] A number of factors contribute to the formation of uric acid calculi in gouty subjects. Almost invariably they present an elevated blood uric acid level and an enlarged metabolic pool of uric acid. Overproduction of uric acid and an increased excretion of urate have been demonstrated in certain patients.[9] Finally, uric acid is concentrated in the kidney. It is a relatively insoluble substance and precipitates readily in acid urine. Thus stone formation is facilitated in gouty patients.

The patient with uric acid calculi and hyperuricemia resembles closely the patient with gout. Hench states that such a patient has definite clinical gout, even though acute gouty arthritis has not yet developed.[10] Talbott has reported a patient who passed uric acid stones for 12 years before developing gouty arthritis.[11] He believes, however, that not all such stone formers need necessarily develop gout. If the patient presented in this report truly has gout, it seems reasonable to assume that he should have had articular symptoms after 18 years. Nevertheless, a therapeutic trial with probenecid, a drug of proved value in gout, appeared to be indicated.

Probenecid (Benemid) inhibits renal tubular reabsorption of urate. The initial effects of its administration consist of a marked increment in urate excretion and a fall of the uric acid blood level.[12] Showers of uric acid crystals may appear and uric acid stones may form. For this reason Talbott[13] has warned against its use in gouty subjects with known calculi. Such possible adverse effects may be minimized by using small initial doses of probenecid, increasing the dose gradually by small increments, increasing the fluid intake, and alkalinizing the urine. The long-term benefits of probenecid administration are a normal blood uric acid level and a decrease in the size of the metabolic pool. In the patient presented, the accomplishment of these ends has halted the tendency toward recurrent uric acid stone formation. The use of probenecid with proper precautions is therefore urged in all instances of recurrent uric acid calculi which have not responded to conservative treatment.

Summary

A patient with recurrent renal uric acid calculi and hyperuricemia without symptomatic gout of 18 years' duration was treated with probenecid. A prompt decrease in the number and frequency of calculi occurred. After 29 months stones stopped forming. Details of management with probenecid, including necessary precautions, have been presented.

SUMMARIO IN INTERLINGUA

Esseva observate un homine de 64 annos de etate con le gravamine de recurrente calculos renal de un duration de 18 annos. Ille evacuava calculos con un frequentia de duo o tres per mense. Tres annos retro, le calculos habeva devenite plus grande, e durante le anno immediatemente precedente illos habeva frequentemente apparite como "arena," i.e. un sol evacuation habeva producite multe calculos de micre dimensiones. Le evacuation esseva precedite per tres dies de dolores lumbar. A vices illo esseva accompaniate de hematuria. Le patiente non habeva un historia de gutta. Repetite essayos de meliorar le condition per dietas povre in purina, per un medication a salicylato, per le fortiate ingestion de fluido, e per un alcalinisation urinari habeva remanite sin successo. Le examine physic revelava hypertension e obesitate, sed alteremente illo non esseva remarcabile. Studios laboratorial revelava hyperuricemia. Esseva constatate que le calculos consisteva de pur crystallos de acido uric. Con le exception del presentia de albuminuria, le tests del function renal monstrava nulle anormalitate.

Un therapia a probenecido (Benemid) esseva instituite. Le dose usate esseva 1,5 g per die. Un effecto immediate esseva notate. Le dimensiones del calculos deveniva de plus in plus micre. Lor apparentia deveniva de plus in plus infrequente, e post 29 menses de un therapia continue lor formation cessava completemente. In le curso del passate cinque menses, le patiente ha evacuate nulle calculos del toto.

Le causa de calculos de acido uric non es cognoscite. Factores de signification in lor production include formation excessive de acido uric, hyperuricemia, augmento del reservas metabolic de acido uric, plus alte concentrationes de acido uric in le renes, e le reduction del solubilitate in urina acide. Le patiente del presente reporto non habeva le componentes arthritic de gutta. Tamen, in altere respectos ille resimilava si pronunciatemente le individuo guttose que un essayo therapeutic con probenecido—un droga de demonstrate merito in casos de gutta—pareva indicate.

Probenecido age per inhiber le reabsorption de acido uric per le tubulos renal. Isto es sequite per un augmento del excretion de uratos, un reduction del nivello de acido uric in le sanguine, e un reduction del magnitude del reserva metabolic de acido uric. In le patiente hic presentate, le effectuation del resultatos listate arrestava le tendentia del formation recurrente de calculos de acido uric. A causa del facto paradoxe que le prime administration de probenecido pote facilitar le formation de calculos, certe precautiones debe esser observate. Istos include le uso de un micre dose initial, le augmento gradual del magnitude del dose, un augmentate ingestion de fluido, e le alcalinisation del urina.

Per consequente, le uso de probenecido (con observation del appropriate precautiones) pote esser recommendate in casos de recurrente calculos de acido uric que non responde al tractamento conservatori.

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SYSTEMIC CANDIDIASIS (MONILIASIS) COMPLICATING TREATMENT OF BACTERIAL ENDOCARDITIS, WITH REVIEW OF LITERATURE AND REPORT OF APPARENT CURE OF ONE CASE WITH PARENTERAL MYCOSTATIN *

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With the advent of antibiotics, acute bacterial endocarditis, which once was nearly always fatal, has been successfully treated. However, with antibiotic therapy there is an increasing number of cases of candidiasis. We wish to report two cases (one ending fatally) with systemic candidiasis complicating the usual antibiotic treatment of bacterial endocarditis. The second case was apparently cured and is alive and well.

Candida infections are commonly seen occurring in the mouth, oropharynx, vagina, rectum, gastrointestinal tract and the skin. A number of cases of bronchopulmonary candidiasis have also been reported.[1, 2] In addition, several cases of Candida meningitis are recorded. However, the incidence of generalized candidiasis is quite rare, and only one case has been reported following treatment for bacterial endocarditis.[3] The first patient with Candida endocarditis was reported by Friedman and Donaldson in 1939[4] as an autopsy finding of fungi in heart valve vegetations. No culture study was done, and the specific organism was not identified. The first proved case of Candida endocarditis (species not identified) was reported by Joachim and Polayes[5] in 1940. This occurred in a narcotic addict who was using opiates intravenously. Eleven

* Received for publication November 21, 1956.
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antemortem blood cultures and postmortem culture were positive for Candida. The next cases reported were by Wikler and associates [6] in 1942. They isolated *Candida parakrusei* from the blood stream of a narcotic addict. Pasternack [7] also reported such a case due to *C. parakrusei* which did not occur in an addict. This latter case is the only example in the literature where there was not preceding antibiotic therapy, direct inoculation, primary blood dyscrasia or intravenous injections.

Zimmerman [8] mentions seven cases of Candida septicemia at Boston Children's Hospital. Five of these cases occurred in leukemic patients and one, in whom he isolated *Candida guilliermondi,* was in an addict. Geiger [3] in the *Yale Journal of Biology and Medicine,* recorded a case due to *Candida albicans* following penicillin treatment for subacute bacterial endocarditis. A number of other cases of systemic candidiasis have been reported since the above articles appeared. All, however, have occurred following antibiotic therapy, or after the use of the steroid hormones. With but a few exceptions, all of these cases have been fatal. Caplan [9] reported a case following a perforated duodenal ulcer; however, the causative fungus was never positively identified as being a member of the Candida genus. Rankin [10] reported a case which occurred following therapy for a staphylococcal abscess on the thigh, and a patient with a Candida peritonitis was reported in the case reports of the *British Medical Journal.*[10] Brown, Propp et al.[11] reported five cases of Candida septicemia, and others have been reported by Wolfe and associates [12] and Kunstadter and co-workers.[13] All of these instances have complicated the massive usage of antibiotics, and except for four, all have been fatal. The first of these was a patient with the bronchopulmonary form of candidiasis treated by immune serum, reported by Hiatt [1]; the second and third were patients with Candida meningitis treated with potassium iodide, reported by Robertson [14] and Zimmerman,[15] respectively; and the fourth, treated by Acti-dione, occurred in a patient after poliomyelitis and was reported by Schaberg et al.[16]

We wish to report two cases of acute bacterial endocarditis with superimposed *C. albicans* septicemia:

Case Reports

Case 1. A 38 year old white female was admitted to the University Hospital on September 23, 1955, with a six weeks' history of weakness and fatigue. Six days prior to admission she had developed chills, fever, headache, backache and stiff neck. Treatment with oral Chloromycetin was instituted, with transient improvement, but as symptoms recurred she was referred to the University Hospital. Physical examination on admission showed a pulse of 100; respiration rate, 18; blood pressure 120/70 mm. of Hg; oral temperature, 101° F. The patient appeared acutely ill and lethargic, and had an inflamed pharynx. Kernig's and Brudzinski's signs were positive, but there were no other neurologic changes. On admission the heart and lungs were clear, but subsequently a systolic murmur was heard, and petechiae and splinter hemorrhages occurred.

The admission white blood count was 8,600, with 76% polys, and by September 25 had risen to 17,000. As the patient continued to have a fever of 105° F., treatment was started with intravenous penicillin, 5,000,000 units per 24 hours, and oral erythromycin and sulfadiazine. When four blood cultures were returned positive for a hemolytic coagulase-positive *Staphylococcus aureus,* the diagnosis of acute bacterial endocarditis was felt to be likely. Subsequently Terramycin was added to the

regimen, sulfadiazine stopped, and the penicillin dosage increased to 25,000,000 units per day. Sensitivity studies showed this combination to be most effective. Blood cultures taken September 29 to October 6 (a total of seven) were all negative, and the patient remained afebrile. On October 5 the penicillin dose was increased to 45,000,000 units per day, and the Terramycin and erythromycin to 2 gm. each. Benamide was tried but had to be discontinued, as the patient developed a dermatitis medicamentosa. On October 12 she developed a fever to 100.5° F., and Achromycin was substituted for Terramycin. An active thrombophlebitis of the basilic vein was found. On October 25 she developed pruritus ani, pruritus vulvae and some vomiting. She had a severe shaking chill, her temperature rose to 102° F., and she complained of great weakness. The penicillin dosage was increased to 80,000,000 units per day, but despite this her temperature remained elevated (to 104° F.) and the nausea and vomiting persisted. Intravenous hydrocortisone was started. Three blood cultures obtained on November 7, and one blood culture on November 9, plus cultures of the pharynx and catheterized urine, were all positive for *C. albicans*. This was verified by subculture on Sabouraud's agar and corn-meal agar, with chlamydospore development on the latter agar. However, the patient continued febrile, lapsed into coma and died on November 9, 1955. Permission for an autopsy was not granted.

Case 2. A 26 year old white male was admitted to University Hospital on April 18, 1956, with a history of a heart murmur, which had been heard at the age of nine years. He had had exertional dyspnea and intermittent cyanosis with clubbed fingers all his life. Six days prior to admission he developed chills, fever, generalized malaise, nausea and vomiting. He was treated with oral and parenteral penicillin, but three days before admission this was stopped following a pruritic erythematous skin eruption. Physical examination on admission showed the patient to be acutely ill. Pulse, 100; respiration rate, 26; blood pressure, 80/60 mm. of Hg: temperature, 103° F. There was a generalized urticarial skin eruption, with superimposed petechiae, mild cyanosis, and clubbed fingers and toes. The pharynx was red, with a white exudate over the tonsillar pillars and slight generalized lymphadenopathy. The lungs were clear but the heart was markedly enlarged, with a harsh, grade 3 systolic murmur heard over the entire precordium. Subsequently, electrocardiograms showed right axis deviation and findings in chest leads suggesting right ventricular hypertrophy. A tentative diagnosis of tetralogy of Fallot was made.

Laboratory data showed on admission a white blood cell count of 12,450 and a hemoglobin of 18.7 gm. Urinalysis showed a 3 plus albumin, 2 to 5 red blood cells and 3 to 4 white blood cells. Spinal fluid examination was negative. It was the impression that the patient had acute bacterial endocarditis; this was supported by a total of six positive blood cultures, taken soon after admission. A coagulase-positive *Staphylococcus aureus* was isolated which was most sensitive to a combination of penicillin and streptomycin.

On admission, treatment was started with 40,000,000 units of penicillin intravenously per day and 1 gm. of streptomycin and 1 gm of dihydrostreptomycin intramuscularly per day. Benamide, 1 gm. orally, was also given. The penicillin allergy was well controlled with intravenous hydrocortisone, 200 mg. per day the first five days, and 50 mg. per day thereafter. The patient responded very well and his temperature promptly fell to normal, with gradual symptomatic improvement. All blood cultures after April 20 were negative for the *Staphylococcus aureus*.

On May 19, 1956, the patient's temperature rose to 104° F., accompanied by chills, fever, malaise and right costovertebral angle tenderness. Urinalysis showed 1 plus albumin, and the sediment was loaded with red blood cells, and showed 8 to 10 white blood cells and 3 to 5 granular casts. Streptomycin was stopped, blood

cultures were obtained, and Gantrisin was added to the regimen. As the patient continued to have a high fever and clinically appeared to be deteriorating, erythromycin intravenously was added to the regimen on May 21. On May 22 many petechiae were seen, plus retinal hemorrhages, diarrhea and oral mucous membrane lesions. A blood culture taken May 19 was reported positive for *C. albicans* (figure 1); erythromycin was stopped, and the patient was started on oral Mycostatin 500,000 units every three hours daily, Mycostatin mouth wash six times a day, and 50% potassium iodide solution, 30 drops three times a day. Urine culture on May 19 was negative. However, on May 24 when further blood cultures were reported positive for *C. albicans,* all antibiotics were stopped and treatment was started with intramuscular Mycostatin, 200,000 units every eight hours.* Subsequently, a total of five blood cultures, plus stool and mouth swab cultures, were reported positive for *C. albicans,* again verified by chlamydospores found on corn-meal agar subcultures. The patient gradually improved on this regimen and after May 29 his temperature remained below 100° F. However, on May 29 he developed an acute thrombophlebitis of the right basilic vein, associated with one temperature elevation to 103° F. This was treated with heparin and phenylindandione, to which he responded

FIG. 1. *Case 2.* Appearance of growth of *C. albicans* on initial blood culture (100 ×).

* Courtesy of Squibb and Company, lot No. 3t 695-714 15-1-B, containing 200,000 units Mycostatin and 2 c.c. diluent of 2% procaine hydrochloride; tween-80, 0.25%, and hydrocortisone, 5 mg.

well. The hydrocortisone was gradually reduced, and was stopped on June 7, 1956, after two intramuscular injections of 25 units of ACTH. The parenteral Mycostatin was stopped on June 8. All subsequent blood cultures, urine, stool and mouth cultures were negative, and except for severe weakness the patient appeared to be making a satisfactory recovery.

The patient was discharged from the hospital at the end of June, 1956. However, re-admission became necessary on July 4, 1956, due to a thrombophlebitis of the leg veins and a low grade fever. This was again successfully treated with anticoagulants, and the patient's temperature fell to normal. Eleven blood cultures were all negative. However, the patient developed an abscess over the sternum at about the level of the fifth costal cartilage, which was drained, and the material obtained was positive on smear and culture for *C. albicans*. Unfortunately, the patient left the hospital against advice and further intensive therapy was not possible. However, he has since been seen in the Out-Patient Clinic. He has remained afebrile, but has developed another superficial abscess just superior to the one noted in the hospital. This also was drained, and the material obtained was again positive in pure culture for *C. albicans*. At present both abscesses remain only as small draining sinuses; the patient is gaining weight and is entirely asymptomatic.

Comment

There are features common to both of the two reported cases. The bacteria producing the septicemia and probable endocarditis in both patients was a coagulase-positive *Staphylococcus aureus*. Both cases were treated with massive amounts of penicillin, plus other broad-spectrum antibiotics, and both were making a satisfactory and uneventful recovery from their bacterial infection. In retrospect it is significant that, after having been afebrile, both patients began to develop a slight rise in temperature approximately one week before abruptly developing a high spiking fever and obvious clinical distress. It seems probable that the *C. albicans* invasion began in both individuals at the time they became febrile after having been under good control for their bacterial endocarditis. Oral candidiasis developed in each instance during the recurrence of fever. Some consideration must therefore be given to the possibility of the occurrence of cutaneous and/or mucocutaneous candidiasis in patients on massive antibiotic therapy as possibly heralding the more serious systemic involvement. *C. albicans* was also found in the urine and pharynx in case 1, and in the pharynx and stool in case 2. This fungus is found in the stool cultures of normal individuals, and it would seem probable that the gastrointestinal tract served as the source of the systemic infection in both of these patients. The broad-spectrum antibiotics administered to both patients are effective in killing the predominantly gram-negative flora of the gastrointestinal tract.

The significance of the first blood culture, which was positive for growth of a member of the Candida genus, was in doubt in both patients. The clinician ordinarily associates the clinical reverse in the course of subacute bacterial endocarditis with a recurrence of the bacterial growth. Case 1 was therefore given an even greater amount of antibiotics when she developed a recurrent spiking fever. It was not until the day of death that the more slowly growing *C. albicans* was observed in the blood cultures.

The Mycostatin which was administered intramuscularly in case 2, and which was apparently effective in eradicating the blood stream infection of *C.*

albicans, was supplied to us for a clinical trial in human systemic North American blastomycosis. This trial was unsuccessful, and some of the remaining Mycostatin was available for use in the second of the two reported cases. The intramuscular injection of this form of Mycostatin has produced extreme muscle soreness and abscess formation at the sites of injection. Our patient tolerated this antifungal substance unusually well, and experienced nothing more than a minor degree of pain and tenderness at the site of injection.

Discussion

Much has been written of *Candida albicans* infection as a complicating disease when intensive antibiotic therapy is used for any purpose. This is especially true when such therapy is administered for prolonged periods of time. The manner in which these antibiotics affect the pathogenicity of fungi is not known, but there are essentially three theories as to their action:[19] (1) that the bacteria in the intestinal tract, the skin and mucous membranes normally consume all of the essential food elements and thus suppress the fungi, which cannot compete successfully with them; (2) that the bacteria synthesize vitamins in the gastrointestinal tract, and in their absence the host's power of resistance might be reduced, also this could be due to a sensitivity response by the host to the antibiotics;[20] (3) that the antibiotics directly stimulate the growth of fungi. In vitro experiments measuring the growth of *C. albicans* found no effect from penicillin, chloramphenicol, streptomycin or Terramycin, but definite increase in the growth of *C. albicans* has been noted in the presence of Aureomycin.[19, 21] This had also been noted clinically.[24]

Acute and subacute bacterial endocarditis are now treated with massive amounts of antibiotics administered over a long period of time. Thus, it would be logical for the fungus *C. albicans* to appear in this disease process as a superimposed infection. It is surprising that this has not occurred with great frequency in the past. To date there has been but one reported case.[3] The possibility remains that this situation may occur more frequently than has been realized, for death from Candida septicemia is rapid once invasion of the blood stream takes place. Thus, the clinician may not have adequate time to evaluate the cause of death fully. Also, it is conceivable that the finding of a growth of a member of the Candida genus in blood cultures may be considered as a contaminant growth, and the full significance of the presence of this yeastlike organism on such a culture may be overlooked by both the laboratory technician and the attending physician. The importance of establishing identification of this fungus as early as possible cannot be overstressed, for it necessitates a complete change in the type of therapy to combat this infectious process. The antibiotics should be discontinued immediately once any species of Candida has been identified in the blood stream. There is also evidence that the corticosteroids act unfavorably in experimental systemic candidiasis, and these substances would seem to be contraindicated.[22, 23, 24]

Candida endocarditis has been considered to be a hopeless disease for which there is no satisfactory cure. Many different agents have been used in its treatment, with but mediocre success. The cutaneous and mucocutaneous forms of candidiasis are now controlled satisfactorily by the use of topical Mycostatin. It has not been possible to prepare this antibiotic substance in a form satisfactory

for parenteral administration. It would therefore appear wise to employ Mycostatin as a preventive measure when long-term massive antibiotic therapy is contemplated on any patient. The authors felt justified in using the experimental crystalline Mycostatin in case 2, since we felt that there was little hope of modifying the course of his otherwise fatal disease process by any other means. We realize that further trial of this form of Mycostatin must be given in order to evaluate properly its effectiveness in systemic candidiasis.

Summary

Two patients with probable bacterial endocarditis due to a coagulase-positive *Staphylococcus aureus* developed *Candida albicans* infection of the blood stream while under treatment for their bacterial infection with massive amounts of broad-spectrum antibiotics. Several antemortem blood cultures were positive in both instances for *C. albicans*. The first patient died rapidly from the superimposed systemic fungus infection. The second patient was successfully treated for the *C. albicans* septicemia by the use of crystalline Mycostatin administered intramuscularly. Since candidiasis is known to occur with increased frequency in individuals receiving broad-spectrum antibiotics for prolonged periods of time, it is surprising that such occurrence has not been reported more frequently during the therapy of bacterial endocarditis. Prophylactic use of oral Mycostatin is advocated at the time broad-spectrum antibiotic therapy is instituted.

Summario in Interlingua

Infectiones per *Candida albicans* es commun in bucca, vagina, recto, vias gastro-intestinal, e pelle. Casos de affection bronchopulmonar e meningee es etiam incontrate. Tamen, un generalisate affection systemic con invasion del currente de sanguine es rar. Le prime demonstrate caso esseva reportate in 1940 e concerneva un narcoticomano. Subsequentemente un numero de altere casos ha essite reportate, sed omnes concerneva norcoticomanos o patientes con dyscrasias del sanguine o occurreva como complication de prolongate therapia con antibioticos a large spectros. Le mechanismo per que antibioticos effectua un potentiation de infectiones per *C. albicans* non es cognoscite, sed le question es coperite per tres theorias. Illos stipula que (1) le bacterios que es normalmente presente in le organismo consume omne le elementos alimentari que es requirite per le fungos e assi rende lor proliferation impossibile, (2) bacterios normalmente presente in le organismo ha le function de synthetisar vitaminas, e in le absentia de illos le resistentia del organismo es reducite, e (3) le antibioticos exerce un effecto directemente stimulatori super le fungos. Es reportate duo casos de un probabile endocarditis bacterial causate per un *Staphylococcus aureus* positive a coagulase. Le duo patientes respondeva ben a un massive tractamento antibiotic, sed in le curso del tractamento illes disveloppava infection del circulation sanguinee per *C. albicans*. Numerose culturas de sanguine esseva positive pro *C. albicans*. Le prime del duo patientes moriva rapidemente ab le systemic infection per le fungo. Le secunde esseva tractate a bon successo pro septicemia per *C. albicans* per administrationes intramuscular de Mycostatina in forma crystallin. Il es surprendente que le reportos de candidiasis systemic post therapia antibiotic pro endocarditis bacterial es restringite a un sol caso additional in le litteratura scrutinate. Le uso prophylactic de Mycostatina oral es recommendate al tempore quando le massive therapia antibiotic con agentes de large spectros es instituite.

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PSEUDOXANTHOMA ELASTICUM WITH GASTRIC HEMORRHAGE: REPORT OF A CASE*

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Review of the literature fails to reveal a case similar to the one reported here of massive gastrointestinal hemorrhage occurring in a pregnant woman during her last trimester.[1, 2, 3, 4, 5] The bleeding was due to pseudoxanthoma elasticum, a very rare cause of gastric hemorrhage. The patient was treated by subtotal gastric resection and subsequently delivered a full term, viable fetus.

Pseudoxanthoma elasticum is the result of elastic tissue degeneration and is characterized by 1 to 5 mm. flat yellowish patches of intradermal changes with a predilection for the flexor folds (axilla, abdomen, neck, upper aspects of the thigh, and the popliteal region). In addition to the lesion of the dermis, the retina may be involved. The retinal lesions are due to degeneration of the many fine elastic fibers in the external portion of the lamina vitrea (Bruch's membrane) of the choroid. When the retinal lesions are present, vision may be slightly impaired in some cases; the involvement may be unilateral or bilateral. Hemorrhages can occur in the retina, with scar tissue formation which may considerably reduce central vision. The retinal changes are also known as angioid streaks, and are usually manifested by irregular, dark, chocolate-colored lines radiating from the disc. Some authorities feel that this disease may be transmitted as a recessive or irregularly dominant hereditary trait. The disease occurs in both sexes equally. The age distribution is from the first through the eighth decade of life, with the highest incidence between the third and fifth.

In 1896 pseudoxanthoma elasticum was named by Darier.[6] The intimate association of pseudoxanthoma elasticum with angioid streaks of the retina was first suggested by Grönblad and Strandberg in 1929.[7, 8] This complex has since been known as the Grönblad-Strandberg syndrome. In 1938 Law published an excellent review on the pathology of angioid streaks.[9]

* Received for publication September 5, 1956.
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The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Air Force Department or the Air Force Service at large.
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Since 1896 there have only been 12 reported cases of gastrointestinal hemorrhage occurring simultaneously with pseudoxanthoma elasticum. The last reported case was by Reinertson and Farber in 1955.[10] The first reported case of micro-anatomic changes of the vascular structures of the intestinal tract was by Prick in 1938.[11] Kaplan and Hartman in 1954 reported the second case of microscopic visceral lesions in this disease.[12] Our case therefore represents the third report of visceral vascular involvement due to this disease proved by histologic sections.

As can be readily understood, the facets in a case of gastrointestinal hemorrhage in pregnancy are many. It is almost impossible to bring out all of the minute details of such a large subject. However, with this in mind, we are presenting the following unusual case report.

Case Report

A 20 year old white married woman was admitted to the hospital on February 1, 1955. At the time of admission she was six months pregnant, her last monthly period having ended July 28, 1954. She had been in good health until the night before admission. She was admitted to the Medical Service following an episode of massive hematemesis and melena. Vague epigastric distress had been noted in the preceding two years. The distress was not related to hunger, food intake or any emotional situation. The past history, social history, dietary history and systemic review were noncontributory. No familial diseases were elicited.

The patient appeared well developed but acutely ill, and had a yellowish pallor of the skin. Temperature was 99.5° F. (oral); blood pressure, 100/70 mm. Hg; pulse, 95; respirations, 22. The skin of the entire neck was studded with 1 to 3 mm. light brownish yellow, irregularly shaped elevations. Transverse folds and thickening of the skin were demonstrated (figure 1). The axillary folds were prominent and the skin in this area lacked elasticity. There were 1 to 5 mm. raised yellowish areas extending to the anterior surface of both shoulder joints. Similar lesions were present in the posterior axillary folds. In both antecubital fossae there were small, 1 to 5 mm. yellowish elevations of the skin which were confluent and formed plaques. These lesions followed the flexor plane. They were soft and located in the dermis of the skin. There was also loss of elasticity in these areas. Similar lesions were noted in the upper thigh below the anterior superior iliac spine; however, these were not so prominent as in the other areas. Similar small areas were noted in the popliteal region and upper sternum. All of the lesions were accentuated by placing slight tension on the skin. Angioid streaks radiated from both optic discs and involved the macula on the left side. The uterus was enlarged to the umbilicus, and the fetal heart tones were heard in the left lower quadrant at 160 per minute. The Rumpel-Leede test was normal. The peripheral pulses (radial, brachial, femoral, popliteal, dorsalis pedis and posterior tibial) were normal.

Admission hemogram showed 7.2 gm. hemoglobin per 100 ml. The hematocrit was 23%. Platelet count showed 200,000 per cubic millimeter. White blood count was 13,600. Urinalysis was normal. Blood urea nitrogen was 27 mg. per 100 ml. Bleeding time was 2 minutes 55 seconds. Lee-White clotting time was 5 minutes. Prothrombin time was 100% of normal. Total serum proteins were normal. Calcium was 10.8 mg. per 100 ml. (5.4 mEq./L.). CO_2 combining power was 56 vol.% (25.4 mEq./L.). Chloride was 594 per 100 ml. (102 mEq./L.). Blood glucose was 120 mg. per 100 ml. Thymol turbidity was 3 units. Cephalin flocculation in 48 hours was normal.

Shortly after admission, surgical and obstetrical consultations were obtained and conservative measures were recommended.

FIG. 1. Neck, demonstrating transverse folds, thickened skin and papular lesions.

Whole blood was started intravenously and nothing by mouth was ordered because of nausea. A careful intake and output record was maintained. On February 2 the patient was not nauseated and had not vomited for 18 hours; she was therefore placed on a Sippy No. 1 regimen, magnesium trisilicate, 8 ml. four times daily, and parenteral Prantal,* 25 mg. every six hours. In addition to this regimen, she was given parenteral estrogen, progesterone, vitamin C and vitamin K in large doses. Blood pressure remained 110/70 mm. Hg. The patient had three large tarry stools on February 2, 1955.

On February 3 the patient had a large emesis of curdled milk with blood clots. Nasal oxygen and phenobarbital (30 mg. four times daily) were begun. Up to this time the patient had received 1,500 ml. of whole blood. After the massive emesis, all feedings were stopped and nasogastric suction was started. An additional 1,500 ml. of blood was administered. During this period the blood pressure fluctuated between 100/70 and 90/50 mm. Hg. The temperature fluctuated between 101° F. and 98.6° F. (oral). The blood urea nitrogen was 22 mg. per 100 ml. The hematocrit was 21% and the hemoglobin 6.4 gm. per 100 ml. On the morning of February 4, after 3,000 ml. of blood had been given, the hemoglobin was 10 gm. per 100 ml., and the hematocrit was 34%. Whole blood was continued. At 2 p.m. the hemoglobin was 8 gm. per 100 ml. and the hematocrit was 26%. The rate of blood administration was increased. At 6 p.m. the hematocrit was 25% and hemoglobin 7.5 gm. per 100 ml. By 10 p.m. patient had received a total of 6,000 ml. of whole blood and the hematocrit was still 25%. Because of the rapid decrease in the hematocrit, and in view of the total amount of blood that had been given, it was felt that this patient had started her gastrointestinal bleeding again.

An upper gastrointestinal series done at 11 p.m. on February 4, 1955, revealed no evidence of a duodenal ulcer but showed a markedly dilated stomach, giving the radiologic impression of a large amount of retained blood in the stomach. The patient was taken to surgery with a hematocrit of 21% and a hemoglobin of 6.4 gm. per 100 ml. She was given vitamin C, vitamin K and calcium gluconate before surgery. She was anesthetized with endotracheal nitrous oxide, ether and oxygen. A paramedian incision was made and the abdominal cavity entered. When the per-

* Prantal, Schering.

itoneum was opened the stomach was found to be approximately the size of a football. The procedure was technically extremely difficult because the uterus extended well up into the epigastric area. Since it was impossible to aspirate all the contents of the stomach through a Levine tube, it was elected to do a gastrotomy and manually express its contents. Enough clotted blood was removed to fill approximately seven emesis basins. A retrocolic isoperistaltic Polya-Hofmeister subtotal gastric resection was done, requiring two hours and 15 minutes. During this time the patient's blood pressure remained stable and at no time dropped below 115/70 mm. Hg. She was given 3,500 ml. of whole blood and 1,000 ml. of 5% dextrose in distilled water during the operative procedure. There was no evidence of duodenal ulcer, and a rapid exploration of the abdominal contents showed them to be within normal limits.

Midway during the operation it was noted that urticaria had developed on the patient's arms. Intravenous Benadryl was given immediately. The urticaria remained for a period of about 45 minutes and then disappeared. There was no concomitant drop in blood pressure or change in pulse rate during this period. The uterus was noted to contract forcefully on one occasion during the closure of the abdomen. Immediately postoperatively, before the patient was removed from the operating table, two smaller contractions were noted by palpation of the lower abdomen. The patient was kept in the recovery room until she recovered from the anesthetic, and was then returned to her room.

Her postoperative course was entirely uneventful. A Levine tube was left in place, and she was maintained entirely on intravenous fluids. An intake-and-output record was kept. Her electrolyte balance was maintained by sodium chloride, potassium chloride and Ringer's solution, as indicated by blood chemistry. A minimal amount of blood was aspirated through the Levine tube for the 24-hour period immediately following the gastric resection; however, this cleared and did not recur. Ambulation was deferred until the third postoperative day because uterine contractions occurred periodically during this time. The patient was continued on stilbestrol, progesterone, mild sedation, penicillin and streptomycin. The Levine tube was removed on the fifth postoperative day, and she was started on clear liquids. Her diet was then graduated to a full purée by the tenth day. Caution was exercised in feeding this patient because of the friability of the gastric stump at the time of anastomosis. At no time during her immediate postoperative course or prior to her discharge from the hospital did this patient exhibit any symptoms of a dumping syndrome.

She was discharged from the hospital on March 4, 1955, and followed in the outpatient department (Medical, Surgical and Obstetrical Clinics). No dietary difficulties were encountered. Pregnancy continued normally, and her hemoglobin remained stabilized at 10 gm. per 100 ml. with a hematocrit of 37%. She had no further evidence of gastrointestinal bleeding.

She was re-admitted to the hospital on April 19, 1955, with ruptured membranes and in early labor. The first stage of labor was approximately four and one-half hours, and she was delivered of a full term, viable baby with the use of saddle block anesthesia, episiotomy and low forceps. Her hemoglobin on this admission was 10.8 gm. per 100 ml., with a hematocrit of 37%. After discharge there were no complications. Periodic examination of the infant, including funduscopic examination, revealed no abnormalities.

The following subsequent studies were done in the Outpatient Department:

X-ray Studies: Upper gastrointestinal series showed 15 to 20% of the stomach remaining. Gall-bladder series, barium enema, postero-anterior and lateral x-rays of the chest and skull series were normal.

Hematology: A complete blood count, including differential, hematocrit, reticu-

locyte count, platelet count, bleeding and clotting time, and clot retraction time, was normal.

Blood Chemistry: Blood chlorides, CO_2 combining power, total serum protein, A/G ratio, blood urea nitrogen, blood calcium, phosphorus and blood sugar were normal.

Liver and Renal Function Tests: Cephalin flocculation, thymol turbidity, bromsulfalein and phenolsulfonphthalein excretion, and urinalysis were normal.

Miscellaneous Tests: Electrocardiogram, psychometric test (Wechsler Bellevue), audiogram and vitamin C level were all normal. Visual fields using the tangent screen and perimeter were performed. The visual field on the right was normal; there were no scotomata. Vision in the left eye was limited to light perception. The night vision test revealed below-average adaptation.

The patient was last seen in the clinic on March 19, 1956, and at that time was doing very well. There were no further changes in the eye grounds or skin. The abdominal wound was well healed. The peripheral pulses were normal.

Examination of the infant, including funduscopic examination, was normal. A skin biopsy of the left antecubital region was normal.

Pathologic Findings: Immediately after surgery the resected portion of the stomach was opened for examination and a large amount of clotted blood was still present among the rugae of the mucosa. The upper one-half of the gastric mucosa was friable and necrotic. It was possible to strip off the mucosa with the finger, and there were many denuded areas. The histopathologic report revealed mucosal and submucosal edema. The veins and capillaries of the mucosa and submucosa were dilated. There were minute ulcerations of the mucosa with overlying fibrin plaques. There was moderately severe degeneration of the elastic tissue of the medium sized arteries (figure 2). The internal lamella was fragmented. Some of the involved blood vessels showed thinning of the vessel wall, with resultant micro-aneurysm formation.

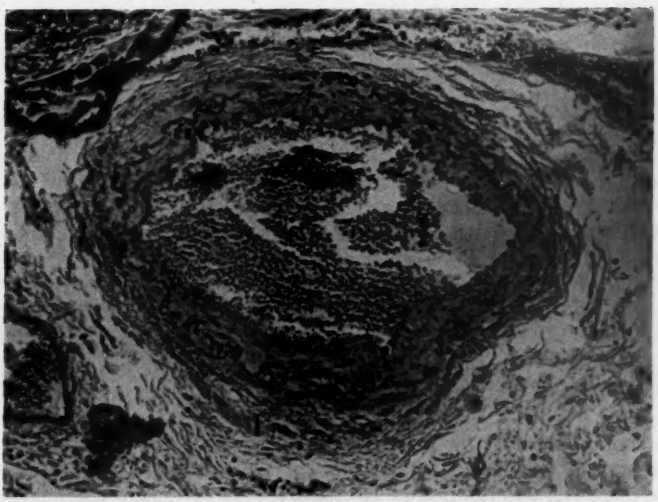

FIG. 2. Photomicrograph section taken from stomach wall, showing moderately severe degeneration of the elastic tissue of a medium sized artery (× 100).

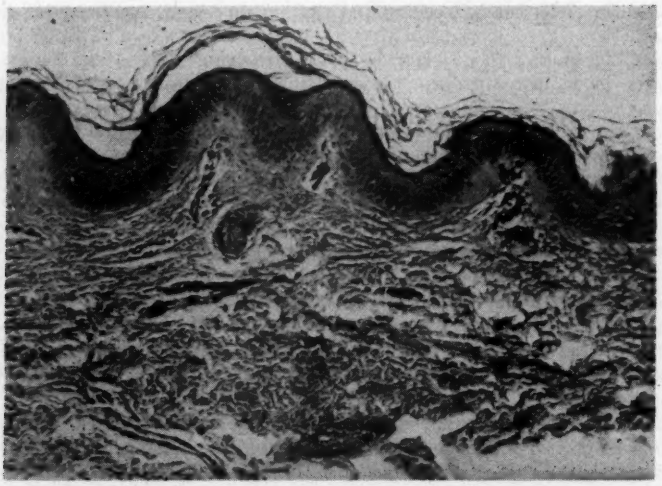

FIG. 3. Photomicrograph of skin taken from right antecubital region, showing swelling, fragmentation, and degeneration of the elastic tissue elements (× 100).

Skin biopsies taken from the neck, axilla, antecubital fossae and thigh revealed swelling, fragmentation and degeneration of elastic tissue elements in the middle and lower dermis (figure 3). The collagen bundles appeared normal. There was no evidence of inflammation. The elastic components of the dermal blood vessels appeared normal. Elastic tissue degeneration was confirmed by elastic tissue stains.

The findings were compatible with pseudoxanthoma elasticum with gastric involvement.

DISCUSSION

That pseudoxanthoma elasticum is a disseminated disease has been reported by others. Revell and Wolff both reported on the peripheral vascular abnormalities that may occur.[13, 14] In their case reports, absence of peripheral pulses was demonstrated. The case reported here did not show this abnormality. It may be that in our patient the disease process has not advanced to the stage where peripheral changes become evident. The elastic tissue changes may initially have a predilection for certain tissues. Whether this selectivity is related to mechanical or to intrinsic factors remains to be proved.

In 1950 Hungarian investigators reported the isolation of elastase from the pancreas that would attack elastic tissue readily. This enzyme was not trypsin, chymotrypsin or carboxypeptidase. It would seem unlikely—though possible—that an abnormality of the pancreas could allow such enzymes, which normally are not present in the blood, to flow into the circulation and to attack certain areas. The discovery of such an enzyme raises the possibility of regulatory mechanisms in the body for elastic tissue.[15]

Our knowledge of this entity will be increased as more cases are reported.

The diagnosis was established in this case only through a thorough investigative program and a high index of suspicion. The diagnosis was made clinically and confirmed by microscopic sections. As to the exact mechanism of the gastric hemorrhage, we believe that it may be due to many factors. In the third

trimester of pregnancy the stomach is usually displaced upward and backward, with subsequent impairment of motility and congestion of the gastric mucosa.[16] Venous obstruction in itself can cause infarction of the stomach.[17] In the case of pseudoxanthoma elasticum, where the arteries of the gastric wall are already damaged, it can be speculated that thrombosis with secondary arterial ischemia may occur. Micro-aneurysms of the smaller arterioles, with rupture, subsequent edema and superficial mucosal ulcerations, can occur. The direct cause of gastric hemorrhage is probably a combination of the above factors.

We feel that the contributing factors which saved this patient were: (1) vigorous supportive and replacement therapy; (2) early diagnostic studies; (3) surgical intervention with subtotal gastrectomy, and (4) careful postoperative management. The case also illustrates that integration of departments in a hospital is necessary for the survival of some patients.

Summary

An unusual case of massive gastrointestinal hemorrhage is presented. The unique features are: (1) hematemesis and melena occurring early in the third trimester of pregnancy; (2) treatment by subtotal gastric resection; (3) subsequent delivery of a full term, viable baby, and (4) pseudoxanthoma elasticum with visceral involvement as the etiologic cause.

This is the first reported case in the literature with the combination of the above circumstances. It also represents the third reported case of pseudoxanthoma elasticum with visceral involvement proved by histologic means. Several factors undoubtedly contributed to the cause of gastric hemorrhage.

Pseudoxanthoma elasticum is a disease primarily involving elastic connective tissue. It is probably transmitted as a recessive or irregularly dominant hereditary trait, and is usually manifested by degenerative changes of the retina, blood vessels, skin and viscera, especially the stomach.

Acknowledgment

We gratefully acknowledge the aid of Dr. John V. Denko, Dr. Lawrence Laiks and Mrs. Mary B. Shelton. For the suggestions of Dr. William C. Dine and Dr. Cleon E. Colgate we are also indebted.

Summario in Interlingua

Pseudoxanthoma elastic es un morbo hereditari que affice elastic histos conjunctive e se manifesta per alterationes degeneratori de derme, retina, vasos sanguinee, e visceres, specialmente le stomacho.

Es presentate un caso inusual de massive hemorrhagia gastrointestinal que occurreva in un juvene gravida durante su ultime trimestre. Derme e retina monstrava le alterationes characteristic de pseudoxanthoma elastic. Mesuras conservatori—i.e. therapia supportative e reimplaciamento de sanguine—esseva mantenite durante 72 horas a partir del hospitalisation del patiente. In despecto del administration de 6.000 cm^3 de sanguine integre, le hematocrite continuava descender. Un serie roentgenographic del region supero-gastrointestinal esseva normal con le exception de marcate grados de dilatation del stomacho. Sub anesthesia general—con le uso endotracheal de oxydo nitrose, ethere, e oxygeno—un retrocolic isoperistaltic resection gastric subtotal de Polya-Hofmeister esseva effectuate. Iste manovra esseva extrememente difficile proque le utero se extendeva marcatemente in le area

epigastric. Le patiente endurava le operation multo ben. Le curso postoperatori remaneva sin incidente. Un mense post le operation illa esseva dimittite. Sex septimanas plus tarde illa esseva hospitalisate de novo in le prime stadios del labores. Subsequentemente illa parturiva un viabile infante nascite a termino. Matre e infante esseva tenite sub observation durante 18 menses in le departimento pro patientes visitante, sed nulle disveloppamento anormal esseva notate. Examines periodic del infante esseva effectuate—incluse ophthalmoscopia e biopsia del pelle. Nulle evidentia del morbo esseva trovate in le infante.

Sectiones histopathologic del resection gastric confirmava le diagnose clinic de pseudoxanthoma elastic. Iste caso representa le tertie reportate de pseudoxanthoma elastic con affection visceral, demonstrate histologicamente.

Le aspectos distinctive e le factores contributori que resultava in le restablimento successose in le presente caso esseva (1) le occurrentia de hematemesis e melena al comenciamento del tertie trimestre, (2) le institution de un vigorose therapia supportative e reimplaciamental, (3) le prompte effectuation de studios diagnostic, (4) le intervention chirurgic con gastrectomia subtotal, (5) le meticulose observation del regime postoperatori, (6) le parturition subsequente de un viabile infante nascite a termino, e (7) pseudoxanthoma elastic con affection gastric como causa etiologic.

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EDITORIAL

INTERMITTENT INSUFFICIENCY OF THE CEREBRAL ARTERIAL CIRCULATION

THE irreparable damage to brain tissue and function which follows a gross failure of its blood supply makes a study of the cerebral circulation and of local disease of its vessels a matter of primary importance. At present there is no way to foresee a cerebral hemorrhage or to control it after it begins, and this has also been true of most cases of extensive thrombosis. Once the damage has been inflicted, nothing can be accomplished except to salvage what functional capacity may have been spared by suitable rehabilitation procedures.

Some encouragement is warranted, however, by recent reports that a careful study may reveal premonitory symptoms of an impending thrombosis which would give an opportunity to institute prophylactic measures if suitable procedures of this sort were available. This has been shown most strikingly in some cases of disease of the basilar vertebral arterial system. The manifestations of intermittent insufficiency of this system, although previously known and reported, have been described and their significance indicated with especial clarity by Millikan and associates.[1] The many vital areas supplied by these arteries and their varied functions, the pons, the brain stem with its numerous closely packed cellular nuclei and fiber tracts, the basal ganglia, large areas of the cerebellum and occipital lobes, make the clinical manifestations highly complex and variable.

In a given case the first recognized symptoms may progress inexorably and rapidly to complete obstruction and fatal infarction. The most characteristic feature, however, is the occurrence of symptoms of local injury coming in numerous successive attacks of relatively abrupt onset and short duration (5 to 15 minutes), and at least for some time, with complete restoration to normal between attacks. Among the symptoms observed are unsteadiness or vertigo (pons), numbness, paresthesias, ataxia and clumsiness; paresis of varying degree of the face, or of one or more limbs, unilateral or bilateral, with exaggerated reflexes and a dorsal plantar response; diplopia, ptosis, disturbed ocular rotation, dimness or complete loss of vision (occipital lobes); confusion, drowsiness or loss of consciousness; dysarthria, slurring of speech, dysphagia, occasionally nausea and vomiting and fever (central in origin). Such disturbances may occur singly, more often in various combinations, and with varying severity. As a rule successive at-

[1] Millikan, C. H., and Siekert, R. G.: Studies in cerebrovascular disease. I. The syndrome of intermittent insufficiency of the basilar arterial system, Proc. Staff Meet., Mayo Clin. **30**: 61–68, 1955.

tacks are similar but not identical. Bilateral involvement or an alternation of the side involved in various attacks, if this does occur, is highly characteristic of a basal lesion.

Symptoms such as these were recorded by Millikan et al.[1] in 10 patients seen early in their illness before any thrombotic accident had occurred. In some cases attacks occurred several times a day, in others much less frequently. They might recur over periods of several days, or for as much as a year, sometimes with long free intervals. In three of these, a fatal attack of thrombosis occurred while under observation, but in six the attacks were arrested and did not recur while under observation, perhaps, one may hope, because of the treatment administered.

Millikan et al.[2] also reported a study of the records of 28 patients who had died from a stroke and showed at autopsy primarily a thrombosis limited to the area supplied by the basilar vertebral arterial system. In 20 of these there had been transitory attacks like those described, from three to many dozen, often scattered over a period of six months to even a year. Recovery in the intervals at first was usually complete. Sooner or later, however, there was some residual damage, and rather quickly the symptoms increased in a stepwise fashion during the attacks until complete obstruction occurred and death followed extensive infarction.

The number of patients with a clear cut syndrome of basilar-vertebral arterial disease is only a small fraction of those with cerebral atherosclerosis. There is evidence, however, that thrombosis of the carotid artery may also be preceded by symptoms suggesting intermittent insufficiency of the internal carotid arterial system. There may be hemiparesis or unilateral sensory disturbances, aphasia if the dominant side is involved, and in about 15 per cent diminution or total loss of vision and diminished blood pressure in the retinal arteries on the side of the lesion. There may be loss of carotid pulsation in the neck, often better demonstrated by palpation in the pharynx. Millikan et al.[3] reported several such cases with brief attacks of about 15 minutes' duration, and complete recovery. In some after two or three episodes persistent hemiplegia developed, in others many mild attacks continued over a few weeks or months before occlusion occurred. How often such premonitory symptoms occur before a thrombosis and how regularly they are followed by occlusion is not yet known.

Symptoms suggesting transient injury to brain tissue are fairly common independent of an impending major vascular accident. One well known example is found in the repeated attacks suffered by some patients with severe malignant hypertension, termed hypertensive encephalopathy by Oppenheimer and Fishberg.[4] Those seen in the earlier acute stage of

[2] Siekert, R. G., and Millikan, C. H.: *Ibid.* II. Some clinical aspects of thrombosis of the basilar artery, *Ibid.* 93–100, 1955.

[3] Millikan, C. H., and Siekert, R. G.: *Ibid.* IV. The syndrome of intermittent insufficiency of the carotid arterial system, *Ibid.* 186–191, 1955.

[4] Oppenheimer, B. S., and Fishberg, A. M.: Hypertensive encephalopathy, Arch. Int. Med. **41**: 264–278, 1928.

the disease are commonly associated with increased intracranial pressure and suffer severe headaches, vomiting, drowsiness, often convulsions and coma.[5] Transient focal disturbances may also be present. More pertinent are the attacks commonly seen in the more chronic cases characterized, in addition to headaches and vertigo, by the abrupt onset of localized weakness or aphasia or sensory disturbances or amaurosis, hemianopsia, astereognosis, sometimes with convulsions but usually with retention of consciousness.[5] Characteristically these are transient and brief, and there is complete restoration to normal between attacks. These, therefore, resemble in many ways the premonitory symptoms seen in the selected groups previously discussed, but they are less stereotyped and there is not the same close association with thrombosis of a major artery.

Even more common in the elderly are symptoms of minor brain injury of almost any type which come on abruptly but which clear up much more slowly and only incompletely. These "little strokes" [6, 7] tend to recur unpredictably as to time, and as to the location and nature of the injury. The residual damage accumulates until it often causes much physical disability and mental deterioration. It is easy to accept the view that these result from thrombotic occlusion of small arteries. This is not a reasonable explanation, however, for similar symptoms which recur dozens of times, last perhaps only 15 minutes, and clear up entirely in the intervals.

Determining the pathogenesis of such attacks becomes of practical importance if we can accept them or some of them as precursors of a major thrombosis which might be averted by suitable treatment. The obvious simple explanation, temporary vasospasm, has been repeatedly advanced for many years, but it has been surprisingly difficult to secure definite proof that such spasm actually occurs, and the matter is still hotly debated.[8, 9, 5, 10] Anatomically the cerebral arteries differ from systemic vessels in having only a thin incomplete muscular layer in the media. The strength of their walls and the capacity to recoil depends largely upon the elastic tissue in the media. They are but feebly responsive to vasoconstrictor agents. There is evidence, however, that they are capable of some degree of vasoconstriction. This has been observed directly in experimental animals in which the exposed vessels were watched through a transparent window inserted in the skull. It has reputedly been observed by neurosurgeons in the course of operations involving the Circle of Willis.

[5] Pickering, G. W.: Transient cerebral paralysis, J. A. M. A. **137**: 423–430, 1948 (May 29).

[6] Fisher, M.: Concerning cerebral arteriosclerosis, J. Am. Geriat. Soc. **2**: 1–18, 1954.

[7] Alvarez, W. C.: The little strokes, J. A. M. A. **157**: 1199–1204, 1955.

[8] Ecker, A.: Emotional stress before strokes: A preliminary report of 20 cases, Ann. Int. Med. **40**: 49–56, 1954.

[9] Wright, I. S., and McDevitt, E.: Cerebral vascular diseases: Their significance, diagnosis and present treatment, including the selective use of anticoagulant substances, Ann. Int. Med. **41**: 682–698, 1954.

[10] Denny-Brown, D.: The treatment of recurrent cerebrovascular symptoms and the question of vasospasm, M. Clin. North America 1951, p. 1457–1474.

There is also clinical evidence to support the possibility of vasoconstriction in certain patients with migraine whose attacks are ushered in by an aura consisting not merely of scotomata and hemianopsia but at times by a transient hemiparesis or hemiplegia, aphasia, or hemianesthesia, suggesting local ischemia of the cerebrum anterior to the occipital lobes. This may be seen in young subjects with at least relatively normal arterial walls, and these attacks may be repeated frequently for many years without permanent injury. Such injury can follow unusually severe attacks, as in Murphy's case of infarction and hemiplegia in a woman of 38,[11] but this is the rare exception.

The weight of evidence, however, indicates that vasospasm probably plays a minor role in these attacks of intermittent circulatory insufficiency. The thickened rigid walls of the arteries in many such cases seem incapable of constriction by the feeble muscle remaining in the wall. Furthermore the use of vasodilators such as papaverine, nicotinic acid, or carbon dioxide inhalations, and blockage by procaine or surgical removal of the stellate ganglia have not yielded any convincingly favorable results.

In patients with these syndromes there is virtually always serious and usually disseminated disease of the cerebral arteries. Atherosclerotic plaques are prone to form at points of bifurcation or branching of the arteries, causing thickening of the wall and marked localized narrowing of the lumen, so that but little additional narrowing may be needed to cause serious ischemia. Even a slight degree of vasoconstriction might suffice. It seems probable, however, that a more important factor is inadequate collateral circulation.

If there is ample collateral circulation and the arteries are reasonably normal it is usually possible to ligate one carotid artery without notable injury to the brain. It is commonly stated, however, that a "normal"—fully open—Circle of Willis is found in only about 50 per cent of human subjects. Therefore if the collateral circulation is reduced by inherent anatomical anomalies or if there is extensive albeit less critical obstruction from atherosclerosis in other cerebral arteries and particularly if both exist, relatively slight fluctuations in collateral flow might precipitate acute ischemia in the distribution of an artery which was almost completely obstructed.

The clinical importance of multiple arterial involvement has been stressed by Hutchinson and Yates.[12] In their series of 40 cases of cerebral vascular disease showing occlusion or marked stenosis at autopsy, 23 showed disease of both vertebral-basilar and carotid systems; 10, of the carotid alone, and 7 of the vertebral alone. The intracranial portions of the arteries were not necessarily obstructed, the lesion sometimes being limited to the segment of the vertebral just above its origin from the subclavian artery

[11] Murphy, J. P.: Cerebral infarction in migraine, Neurology **5**: 359–361, 1955.
[12] Hutchinson, E. C., and Yates, P. O.: Carotico-vertebral stenosis, Lancet **1**: 2–8, 1957.

in the neck or to the internal carotid just above the bifurcation. In no case was infarction found with disease limited to one carotid. For this reason they have suggested the term "carotico-vertebral stenosis."

Fluctuations in blood pressure must be considered. Undoubtedly a fall in blood pressure can precipitate ischemia, but this seems inadequate to explain most of the attacks of intermittent insufficiency. As a rule no adequate parallelism between them is observed.

Hemorrhage into or under a plaque or swelling from some other cause has been suggested, but this can not well explain a rapid succession of brief attacks.

The formation of a thin layer of thrombus over a plaque, or tiny emboli from such a friable thrombus temporarily blocking the orifice of small arterial branches has also been suggested.[13] Similar objections to this arise, although it might well apply to some subjects in whom only a very few premonitory attacks occur. The frequent chronological relationship of transitory ischemia to subsequent thrombosis does indicate, however, that there may be some relationship, perhaps less direct and obvious, between them, and it has naturally suggested that anticoagulants might be useful therapeutically.

For a decade anticoagulants have been used, especially by Wright and his associates,[14] in cases of recurring cerebral embolism and secondary thrombosis arising from thrombotic lesions elsewhere, commonly from the heart, particularly if fibrillating, when damaged by chronic rheumatic endocarditis, hypertension, atherosclerosis or myocardial infarction. They have recently summarized their results [15] in 90 patients followed for substantial periods. In brief, based on the number of patient-months of observation, the number of "thrombo-embolic episodes" of all sorts and also the number of cerebral attacks in patients receiving treatment were reduced to from one-third to one-fourth of the number occurring when not under treatment. Treatment was considerably more effective if continuous than if interrupted.

In addition in 10 patients with intermittent insufficiency of the cerebral circulation, the number of ischemic attacks was reduced by about 75 per cent while under treatment.

Although several other favorable reports have appeared limited to one or a very few cases, the series recently summarized by Millikan et al.[16] is the most extensive yet available, and it confirms their earlier favorable preliminary reports. Ischemic attacks ceased in 90 of 94 adequately treated

[13] Millikan, C. H., et al.: Studies in cerebrovascular disease. V. The use of anticoagulant drugs in the treatment of intermittent insufficiency of the internal carotid arterial system, Proc. Staff Meet., Mayo Clin. **30**: 578–586, 1955.

[14] Foley, W. T., and Wright, I. S.: The treatment of cerebral thrombosis and embolism with anticoagulant drugs: preliminary observations, M. Clin. North America **34**: 909–924, 1950.

[15] McDevitt, E., et al.: Use of anticoagulants in treatment of cerebral vascular disease. Ten years experience in treatment of thromboembolism, J. A. M. A. **166**: 592–597, 1958.

[16] Millikan, C. H., et al.: Anticoagulant therapy in cerebral vascular disease—current status, J. A. M. A. **166**: 584–592, 1958.

patients with intermittent insufficiency of the vertebral basilar system, and none went on to occlusion. They ceased in 82 of 85 patients with intermittent insufficiency of the internal carotid system, although one went on to occlusion. In a group of patients in whom thrombosis of the vertebral basilar system was believed to have begun, 9 of 107 treated died, a mortality of 8 per cent, whereas 18 of 31 untreated died, a mortality of 58 per cent. In those thought to have beginning thrombosis in the internal carotid group, 29 of 31 were arrested and 2 progressed, 6 per cent. In 17 similar untreated cases, 6 (35 per cent) progressed to hemiplegia or died.

The authors stress the importance of a critical study and precise diagnosis before initiating such treatment. Tumor and other gross lesions must be excluded. Presumably too it would be harmful in cerebral hemorrhage. Strokes due to cerebral thrombosis are considerably more frequent than those due to cerebral hemorrhage, and the latter can usually be recognized by the more fulminant course, closer association with marked hypertension and often by finding blood in the spinal fluid.

Anticoagulants should not be given to everyone with a damaged brain. Only prevention or arrest can be hoped for, and if damage is complete and progress has stopped, treatment is useless. If the carotid system is involved, Millikan advises watching for a few hours if there is doubt as to whether the condition is advancing. With the basilar system, however, because of the treacherous course and high mortality, immediate treatment is advised as an emergency procedure.

The usual contraindications for anticoagulant treatment should be considered, and the patients carefully watched, with frequent determinations of the prothrombin time. Treatment seems to be ineffective unless substantial prolongation of the prothrombin time is maintained. How long treatment must be continued seems uncertain but apparently it should be for many months. In some cases a fatal thrombosis followed soon after treatment was stopped.

Millikan quotes M. Fisher and J. S. Meyer (personal communications) as having had favorable results in similar studies not yet reported.

Further confirmation of these observations is needed to determine the reliability of these clinical syndromes as diagnostic guides as well as the practical value of such treatment. The regularity with which the premonitory symptoms were arrested, however, and major thrombosis apparently deferred is quite impressive. How regularly and how long such a respite may be maintained will require a statistical study of large series of cases over longer periods and with more adequate controls. It seems evident that there are substantial and inescapable limitations to the accomplishments that may reasonably be anticipated in such patients. Any means, however, which will not merely prolong life but which will maintain such subjects in a state of useful activity and comfort will be a welcome advance.

PAUL W. CLOUGH, M.D.

REVIEWS

The Leukemias: Etiology, Pathophysiology, and Treatment. Henry Ford Hospital International Symposium. Edited by JOHN W. REBUCK, FRANK H. BETHELL, and RAYMOND W. MONTO. 711 pages; 15.5 × 24 cm. Academic Press, Inc., New York. 1957. Price, $13.00.

The editors have collected the papers and discussions presented at an international symposium on leukemia, sponsored by the Henry Ford Hospital in Detroit, May 8–10, 1956. Their publication in book form brings together the results of current major investigative approaches in leukemia research and gives the interested reader an unsurpassed reference volume.

The book is divided into eight sections with a number of reports in each section: I. The Leukemic Cell, Its Structure and Antigenicity; II. Genetic and Environmental Factors in the Transmission of Leukemia; III. Radiation Biology of Leukocytes; IV. The Leukemias and the Malignant Lymphomas; V. Leukocytic Physiology; VI. Metabolism of Amino and Nucleic Acids in the Leukemias; VII. Further Biochemical Considerations in the Leukemias; and VIII. Nucleic Acids as the Target for Chemotherapy; Mechanisms of Drug Action and Resistance.

Fifty-seven investigators participated. The reports are authoritative and up to date. Some of the material had not been published previously and represents work in progress. Extensive bibliographies after each paper add to the value. The discussions are provocative and stimulating. The printing and reproduction of illustrations are excellent.

The book is highly recommended for hematologists and all those interested in the basic problems of cancer research.

C. L. SPURLING, M.D.

Radicular Syndromes, With Emphasis on Chest Pain Simulating Coronary Disease. By DAVID DAVIS, B.S., M.D. 266 pages; 14 × 20.5 cm. The Year Book Publishers, Inc., Chicago. 1957. Price, $6.50.

Increasing awareness of the fact that symptoms such as chest pain, vertigo and respiratory distress may be manifestations of root compression rather than of coronary disease prompted the author to reëvaluate his clinical experience with patients suspected of coronary disease, to consult orthopedic surgeons, and to study the literature. This text is a summary of his findings. The skeletal and neurological basis for cervico-thoracic root syndromes is described, the clinical characteristics of root pain are considered, and cases are cited to illustrate many of these. The differential diagnosis is presented and the treatment of the radicular syndromes is discussed.

This is a small but valuable book. It is well written, and serves to emphasize the fact that while clinical coronary disease may be present without any electrocardiographic abnormalities, the physician is obligated to consider non-cardiac as well as cardiac causes of chest pain in the differential diagnosis, and radicular syndromes rank high among the former. This volume is recommended to all who are confronted with the problem of clinical recognition of coronary disease.

S. S.

Drug Resistance in Micro-Organisms: Mechanisms of Development. A Ciba Foundation Symposium. Edited by G. E. W. WOLSTENHOLME and CECILIA M. O'CONNOR. 352 pages; 21 × 14.5 cm. Little, Brown and Co., Boston. 1957. Price, $9.00.

In March of 1957 a symposium on the mechanisms of development of drug resistance in micro-organisms was held under the auspices of the Ciba Foundation. This book is the record of the papers presented with the discussion of those papers.

Dean, Hinshelwood, Demerec, Cavalli-Sforza, Lederberg, Hughes, Yudkin, Davis, Hayes are some of the expert men in this field who participated.

The battle line is immediately drawn between those who maintain that bacterial resistance is a function of random mutation with environmental selection and those who hold that physiological adaptation is the mechanism of resistance. This mutation-adaptation controversy motivates the conference and is mollified only by the suggestion that more than one mechanism may be effective with different organisms under differing circumstances.

The papers are well selected to illustrate impressive work and thought in the field and the book must be strongly recommended to those with a deep interest in microbiology and chemotherapeutics.

PATRICK B. STOREY, M.D.

La Puberté: Étude Clinique et Physiopathologique. 2nd Ed. By GUY LAROCHE, A. ASSAILLY, H. BRICAIRE, G. BROUET, E. FERRON, G. HUC, CL. LAROCHE, J. LEPRAT, P. MAURICE, H. SIMONNET, R. TOURNEUR and J. TRÉMOLIÈRES. 395 pages; 16.5 × 25.5 cm. (paper-bound). Masson et Cie., Paris. 1956. Price, 2.800 fr.

This treatise, dealing with the clinical and physiopathologic aspects of puberty, is presented in an effective, direct and simple style.

There are ten chapters, each written by an authority in his particular field. The first chapter introduces the reader to the "Mechanism of Puberty" and deals with the role of gonadal and extra-gonadal factors in the transition of the organism from "an infantile state to the adult state."

The subsequent chapters deal with Puberty and Tuberculosis, Anorexia, Simple Goiter, The Heart, Infantilism, Nutrition, Physical Measurements, Psychologic and Psychopathologic Aspects.

The material is presented in an orderly fashion; the illustrations are well chosen and appropriate to the subject matter; the bibliography is extensive in coverage.

Puberty, as stated in the introduction, is of increasing interest to physicians and to the public at large. The reviewer is in complete agreement with this statement and commends the author and his collaborators for their timely and informative publication.

J. E. B.

The Physiologic Basis of Gastrointestinal Therapy. By HEINRICH NECHELES, M.D., Ph.D., F.A.C.P., and MARTIN M. KIRSHEN, M.D., F.A.C.P. 300 pages; 14 × 22.5 cm. Grune and Stratton, New York. 1957. Price, $8.75.

At the request of their former students, the authors have assembled the gastrointestinal physiologic lectures into one edited volume making it one of the most complete texts available. The normal and abnormal physiologic processes of the intestinal tract are briefly but concisely covered and analyzed. The chapters concerning innervation and motility are especially stimulating.

The book is didactic and not easy to read because practically every sentence is a statement of fact or theory. The occasional mention of clinical experiences flavors the text and keeps it from being completely dry. Subject matter includes current pharmacologic-physiologic problems such as carcinoid tumors, hepatic coma, and glucagon. Controversial subjects are presented as such and the authors do not become involved other than to reject unphysiologic reasoning. Each chapter has a more than adequate bibliography.

There has long been a need for such a text because of its practical clinical application. Anyone interested in obtaining a better understanding of gastrointestinal diseases and therapy will appreciate the book.

H. F. R.

Tumors of the Cardiovascular System (Atlas of Tumor Pathology, Section III, Fascicle 7). By BENJAMIN H. LANDING, M.D., Pathologist, The Children's Hospital, Cincinnati, Ohio, and SIDNEY FARBER, M.D., Professor of Pathology, Harvard Medical School, at The Children's Hospital. 138 pages; 20 × 26 cm. (paper-bound). Published by the Armed Forces Institute of Pathology, 1956, under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the Division of Medical Sciences of the National Academy of Sciences, National Research Council, Washington, D. C. Price, $1.50.

This section of the Atlas of Tumor Pathology is devoted to tumors of the cardiovascular system. As stated in the introduction, tumors of the heart are infrequent and tend to be well defined, whereas tumors of the blood vessels are more frequent, less well defined, and usually not malignant. This volume consists primarily of a collection of beautiful illustrations of such tumors, with a brief written text presenting pertinent information concerning definition, natural history, description and treatment of the tumors, and a few selected references. This volume is recommended to pathologists and to medical and surgical specialists who must deal with the tumors described.

S. S.

Practical Forensic Medicine. By FRANCIS E. CAMPS, M.D., and W. B. PURCHASE, C.B.E., M.C., M.B., D.P.H. 541 pages; 15.5 × 24 cm. The Macmillan Company, New York. 1957. Price, $13.50.

These authors are among the outstanding medicolegal experts in England today. Their authoritative and clearly written text is divided into three principal sections: Forensic Medicine, Toxicology, and Appendices. The last are eleven in number and include a listing of important British laws concerning poisons, specimen forms for various medicolegal reports, directions for properly completing death certificates, rules governing the performance of coroner's autopsies and a glossary of terms in frequent medicolegal use. The first section consists of 26 chapters presenting various medicolegal topics in alphabetic order from Abortion, through Alcoholic Intoxication, Asphyxia, Bastardy Proceedings, Coroner, Injuries, Medicolegal Autopsies, Medical Negligence, Sexual Offenses, to Wounds, to mention a few. Where pertinent the relevant law is presented followed by a concise but remarkably complete, for the size of the book, discussion of the practical points in recognizing and collecting medicolegal evidence with descriptions of the gross and rarely the microscopic pathology of the common types of injuries, their complications and medicolegal problems posed.

The toxicology section follows a similar pattern with sections on the Law of Poisons, Drug Addiction, Poisoning generally and the Common Poisons with their symptomatology, diagnostic findings, treatment and postmortem recognition. No effort is made to present technical methods for isolation or identification of the poisons. Seventy-nine pages are devoted to a Collectanea of Poisons showing in tabular form the normal use of the chemicals, symptoms of poisoning, fatal doses, typical postmortem findings and the optimal specimens to be collected for chemical analysis for verification or identification of the poisonous agent. This section best displays the authors' talents for reducing a great deal of information to a readily and rapidly understandable form. Throughout the book there are excellent illustrations chosen usually to display a single point and the more effective for their simplicity. Frequent sketches augment the photographs in illustrating the mechanism of production of various injuries. Each section furnishes a list of selected texts and literature citations for further detailed reading about the subject matter.

This reviewer commends the book to doctor, lawyer, police and lay reader because of its concise presentation of the essentials of a large subject in a particularly clear and practical manner.

RUSSELL S. FISHER, M.D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Aldosterone: An International Symposium. Edited by ALEX F. MULLER, M.D., and CECILIA M. O'CONNOR, B.Sc. 232 pages; 22.5 × 14.5 cm. 1958. Little, Brown and Company, Boston. Price, $8.00.

Arteriosklerose. Nauheimer Fortbildungs-Lehrgänge Bd. 23. Fortbildungslehrgang in Bad Nauheim vom 27. bis 29. September 1957. Herausgegeben von Vereinigung der Bad Nauheimer Ärzte. 137 pages; 24.5 × 17 cm. (paper-bound). 1958. Verlag von Dr. Dietrich Steinkopff, Darmstadt. Price, brosch. DM 16,–; geb. DM kart.

The Atomic Age and Our Biological Future. By H. V. BRØNSTED; translated by E. M. HUGGARD. 80 pages; 19 × 12.5 cm. 1957. Philosophical Library, New York. Price, $2.75.

The Brain and Human Behavior: Proceedings of the Association, December 7 and 8, 1956, New York, N. Y. Research Publications, Association for Research in Nervous and Mental Disease. Vol. XXXVI. Editors: HARRY C. SOLOMON, M.D., STANLEY COBB, M.D., and WILDER PENFIELD, M.D. 564 pages; 23.5 × 15.5 cm. 1958. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents. Price, $15.00.

The Chemistry and Biology of Mucopolysaccharides: Ciba Foundation Symposium. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and MAEVE O'CONNOR, B.A. 328 pages; 21 × 14 cm. 1958. Little, Brown and Company, Boston. Price, $8.50.

Endocrine Aspects of Breast Cancer: Proceedings of a Conference Held at the University of Glasgow, 8th to 10th July 1957. Edited by ALASTAIR R. CURRIE, B.Sc., M.B., F.R.C.P.Ed., Senior Lecturer in Pathology, University of Glasgow, etc.; foreword by C. F. W. ILLINGWORTH, C.B.E., M.D., Ch.M., F.R.C.S.Ed., F.R.F.P.S., Regius Professor of Surgery, University of Glasgow, etc. 340 pages; 22.5 × 14.5 cm. 1958. The Williams & Wilkins Company, Baltimore, exclusive U. S. Agents. Price, $8.50.

Fat Consumption and Coronary Disease: The Evolutionary Answer to This Problem. A Basic Approach to the Prevention and Arrest of Coronary Disease. By T. L. CLEAVE, M.R.C.P. (Lond.), Surgeon Captain, Royal Navy; with a foreword by PERCY STOCKS, C.M.G., M.A., M.D. (Camb.), F.R.C.P. (Lond.), F.S.S., Senior Research Fellow, British Empire Cancer Campaign, etc. 40 pages; 18.5 × 12.5 cm. (paper-bound). 1958. Philosophical Library, New York. Price, $2.50.

Geschlecht und Krankheit. By PROFESSOR DR. h. c. MAX BÜRGER. 516 pages; 23 × 16 cm. 1958. J. F. Lehmanns Verlag, München. Price, DM 60.–

The Guinea Pig in Research: Biology—Nutrition—Physiology. By MARY ELIZABETH REID, Ph.D., Laboratory of Nutrition and Endocrinology, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare, Bethesda, Maryland. 87 pages; 23 × 15 cm. (paper-bound). 1958. Human Factors Research Bureau, Inc., Washington, D. C. Price, $2.00.

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